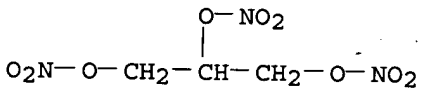
RN 55-63-0 REGISTRY
CN 1,2,3-Propanetriol, trinitrate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Nitroglycerin (8CI)
OTHER NAMES:
CN 1,2,3-Propanetriyl nitrate
CN Angibid
CN Anginine
CN Angiolingual
CN Angorin
CN Blasting oil
CN Cardamist
CN Chitamite
CN Deponit
CN Epinitril
CN Gilucor nitro
CN Glonoin
CN Glycerin trinitrate
CN Glycerol trinitrate
CN Glyceryl nitrate
CN **Glyceryl trinitrate**
CN GTN
CN Klavikordal
CN Lenitral
CN Minitran
CN Minitran (nitroglycerin)
CN Myoglycerin
CN NG
CN Niglin
CN Niglycon
CN Nitora
CN Nitrin
CN Nitrine
CN Nitrine-TDC
CN Nitro-Bid
CN Nitro-Dur
CN Nitro-lent
CN Nitro-Span
CN Nitrocardin
CN Nitroderm
CN Nitroglycerine
CN Nitroglycerol
CN Nitroglyn
CN Nitrol
CN Nitrol (pharmaceutical)
CN Nitrolan
CN Nitroletten
CN Nitrolingual
CN Nitrolowe
CN Nitromel
CN Nitrong
CN Nitropercuten
CN Nitrorectal
CN Nitroretard
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS 3D CONCORD
DR 8013-23-8, 9010-02-0, 105469-31-6, 80066-48-4
MF C3 H5 N3 O9
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU,



```
     FILE 'REGISTRY' ENTERED AT 00:58:46 ON 04 NOV 2002
L1             1 S GLYCERYL TRINITRATE/CN

     FILE 'CAPLUS, WPIDS, MEDLINE, CANCERLIT' ENTERED AT 00:59:59 ON 04 NOV
     2002

     FILE 'REGISTRY' ENTERED AT 01:00:16 ON 04 NOV 2002
                SET SMARTSELECT ON
L2           SEL L1 1- CHEM :      77 TERMS
                SET SMARTSELECT OFF

     FILE 'CAPLUS, WPIDS, MEDLINE, CANCERLIT' ENTERED AT 01:00:17 ON 04 NOV
     2002
L3         273142 S L2/BI
L4          32678 S L3 (L) (CANCER? OR ANTICANCER? OR ANTINEOPLASTIC? OR ANTITUMO
L5         315922 S (CANCER? OR MALIGNAN? OR TUMOR? OR NEOPLAS?) (10A) (PREVENT?
L6           5062 S L4 AND L5
L7           4551 S (TRINITRATE OR GLYCERYL NITRATE OR GTN OR NITROGLYCERIN# OR N
L8             42 S L7 AND L6
L9             22 DUP REM L8 (20 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 01:14:57 ON 04 NOV 2002

     FILE 'CAPLUS, WPIDS, MEDLINE, CANCERLIT' ENTERED AT 01:21:15 ON 04 NOV
     2002
L10          32672 S L4 NOT (GTN OLIGODEOXY?)
L11           5056 S L6 NOT (GTN OLIGODEOXY?)
L12           4804 S L11 NOT (NG (4A) ARGININE)
L13             52 S (TRINITRATE OR GLYCERYL NITRATE OR NITROGLYCERIN# OR NITROGLY
L14             36 S L13 NOT L9
L15             23 DUP REM L14 (13 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 01:24:53 ON 04 NOV 2002

=> d que l9; d que l15
L1             1 SEA FILE=REGISTRY GLYCERYL TRINITRATE/CN
L2               SEL  L1 1- CHEM :      77 TERMS
L3         273142 SEA L2/BI
L4          32678 SEA L3 (L) (CANCER? OR ANTICANCER? OR ANTINEOPLASTIC? OR
                  ANTITUMOR? OR TUMOR? OR MALIGNAN?)
L5         315922 SEA (CANCER? OR MALIGNAN? OR TUMOR? OR NEOPLAS?) (10A)
                  (PREVENT? OR PROPHYLA? OR REDUC? OR INHIBIT?)
L6           5062 SEA L4 AND L5
L7           4551 SEA (TRINITRATE OR GLYCERYL NITRATE OR GTN OR NITROGLYCERIN#
                  OR NITROGLYCEROL OR NITROGLYN) (35A) (PREVENT? OR PROPHYLA? OR
                  REDUC? OR INHIBIT?)
L8             42 SEA L7 AND L6
L9             22 DUP REM L8 (20 DUPLICATES REMOVED)



L1             1 SEA FILE=REGISTRY GLYCERYL TRINITRATE/CN
L2               SEL  L1 1- CHEM :      77 TERMS
L3         273142 SEA L2/BI
L4          32678 SEA L3 (L) (CANCER? OR ANTICANCER? OR ANTINEOPLASTIC? OR
                  ANTITUMOR? OR TUMOR? OR MALIGNAN?)
L5         315922 SEA (CANCER? OR MALIGNAN? OR TUMOR? OR NEOPLAS?) (10A)
                  (PREVENT? OR PROPHYLA? OR REDUC? OR INHIBIT?)
L6           5062 SEA L4 AND L5
L7           4551 SEA (TRINITRATE OR GLYCERYL NITRATE OR GTN OR NITROGLYCERIN#
                  OR NITROGLYCEROL OR NITROGLYN) (35A) (PREVENT? OR PROPHYLA? OR
                  REDUC? OR INHIBIT?)
L8             42 SEA L7 AND L6
L9             22 DUP REM L8 (20 DUPLICATES REMOVED)
```

```
L11         5056 SEA L6 NOT (GTN OLIGODEOXY?)
L12         4804 SEA L11 NOT (NG (4A) ARGININE)
L13           52 SEA (TRINITRATE OR GLYCERYL NITRATE OR NITROGLYCERIN# OR
                 NITROGLYCEROL OR NITROGLYN) AND L12
L14           36 SEA L13 NOT L9
L15           23 DUP REM L14 (13 DUPLICATES REMOVED)

=>
```

=> d 1-22 bib hit

L9 ANSWER 1 OF 22 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-362397 [39] WPIDS
DNC C2002-102624
TI Drug composition for treating myopia contains nitric oxide synthase substrate and/or nitric oxide donor, or immune nitric oxide inducing inhibitors and/or immune nitric oxide synthase activity inhibitors of arginine derivatives.
DC B05
IN CHENG, T T S; CHIOU, G C Y
PA (YONG-N) YONG GUANG PHARM CO LTD
CYC 91
PI WO 2002024191 A1 20020328 (200239)* ZH 37p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000075035 A 20020402 (200252)
ADT WO 2002024191 A1 WO 2000-CN286 20000920; AU 2000075035 A AU 2000-75035 20000920, WO 2000-CN286 20000920
FDT AU 2000075035 A Based on WO 200224191
PRAI WO 2000-CN286 20000920
TECH UPTX: 20020621
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The NOS substrate comprises 4-phenyl-3-N-oxyoxadiazolecarbonitrile, arginine, canavanine, Nalpha-acylated arginine or their salts or esters, particularly L-arginine, L-canavanine or Nalpha-acyl-L-arginine, especially Nalpha-benzoyl-L-arginine ethyl ester, di-O-(Nalpha-L-benzoyl-L-arginine) glycol, tri-O-(Nalpha-benzoyl-L-arginine ethyl ester) glycerine, or L-arginine, L-canavanine or Nalpha-benzoyl-L-arginine ethyl ester.
The NO donor comprises minoxidil, hydralazine, **nitroglycerine**, isosorbide or its ester, nitroprusside, nitrite salt, glutathione derivative and N-nitropyrazole derivative, particularly minoxidil, hydralazine, **nitroglycerine**, isosorbide nitrate, nitroprusside, sodium nitrite, glutathione, 5-nitrosoglutathione, N-nitropyrazole, 3,5-dimethyl-N-nitropyrazole or 3-methyl-N-nitropyrazole.
The immune NOS-inducing **inhibitor** comprises polyamine, calcium antagonist, platelet-deriving growth factor, platelet-activating factor antagonist, **tumor**-necrosis factor antibody, interleukin, protein kinase **inhibitor** or tyrosine kinase **inhibitor**; particularly argino-aldehyde, dihydropyrimidine, omega-(N,N'-diethylamino)-n-alkyltrimethylbenzoate, platelet-deriving growth factor, platelet-activating factor antagonist, **tumor**-necrosis factor antibody, interleukins-4, 8, 10, 13 and 1ra, protein kinase inhibitor or lukeluomeng (sic).
The immune NOS-inducing inhibitor comprises L-arginine analogs, methylene blue, aminoguanidine, S-methylisothiourea, particularly **NG**-methyl-L-arginine, **NG**-amino-hemoarginine, **NG**-amino-L-arginine, **NG**-nitro-L-arginine, dimethylarginine, methylene blue, aminoguanidine or S-methylisothiourea.
The composition also contains anticholinergic drugs, cycloplegic drugs and/or sympathomimetic drugs. The anticholinergics comprise atropine or piroheptine. The cycloplegics comprise cyclopentamine or tropicamide, and the sympathomimetics comprise phenylephridine or adrenaline.

L9 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
AN 2002:721679 CAPLUS
TI Oxygen-mediated Regulation of Tumor Cell Invasiveness. Involvement of a nitric oxide signaling pathway
AU Postovit, Lynne-Marie; Adams, Michael A.; Lash, Gendie E.; Heaton, Jeremy P.; Graham, Charles H.

CS Department of Anatomy and Cell Biology, Queen's University, Kingston, ON, K7L 3N6, Can.
SO Journal of Biological Chemistry (2002), 277(38), 35730-35737
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB **Tumor** hypoxia is assocd. with a poor prognosis for patients with various **cancers**, often resulting in an increase in metastasis. Moreover, exposure to hypoxia increases the ability of breast carcinoma cells to invade the extracellular matrix, an important aspect of metastasis. Here, we demonstrate that the hypoxic up-regulation of invasiveness is linked to reduced nitric oxide signaling. Incubation of human breast carcinoma cells in 0.5% vs. 20% oxygen increased their in vitro invasiveness and their expression of the urokinase receptor, an invasion-assocd. mol. These effects of hypoxia were inhibited by nitric oxide-mimetic drugs; and in a manner similar to hypoxia, pharmacol. inhibition of nitric oxide synthesis increased urokinase receptor expression. The nitric oxide signaling pathway involves activation of sol. guanylyl cyclase (sGC) and the subsequent activation of protein kinase G (PKG). Culture of **tumor** cells under hypoxic conditions (0.5% vs. 20% oxygen) resulted in lower cGMP levels, an effect that could be **prevented** by incubation with **glyceryl trinitrate**. Inhibition of sGC activity with a selective blocker or with the heme biosynthesis inhibitor desferrioxamine increased urokinase receptor expression. These compds. also **prevented** the **glyceryl trinitrate**-mediated suppression of urokinase receptor expression in cells incubated under hypoxic conditions. In contrast, direct activation of PKG using 8-bromo-cGMP prevented the hypoxia- and desferrioxamine-induced increases in urokinase receptor expression as well as the hypoxia-mediated enhanced invasiveness. Further involvement of PKG in the regulation of invasion-assocd. phenotypes was established using a selective PKG inhibitor, which alone increased urokinase receptor expression. These findings reveal that an important mechanism by which hypoxia increases **tumor** cell invasiveness (and possibly metastasis) requires **inhibition** of the nitric oxide signaling pathway involving sGC and PKG activation.

L9 ANSWER 3 OF 22 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-066405 [09] WPIDS
DNC C2002-019742
TI Use of nitric oxide mimetics for **inhibiting** or **preventing** a **malignant** cell phenotype, useful for **preventing**, monitoring or treating **cancer**.
DC B06
IN ADAMS, M A; GRAHAM, C H; HEATON, J P W; POSTOVIT, L
PA (TOOH) UNIV QUEENS KINGSTON; (ADAM-I) ADAMS M A; (GRAH-I) GRAHAM C H; (HEAT-I) HEATON J P W; (POST-I) POSTOVIT L
CYC 94
PI WO 2001080890 A2 20011101 (200209)* EN 54p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ YU ZA ZW
AU 2001050221 A 20011107 (200219)
US 2002040059 A1 20020404 (200227)
ADT WO 2001080890 A2 WO 2001-CA566 20010426; AU 2001050221 A AU 2001-50221 20010426; US 2002040059 A1 Provisional US 2000-199757P 20000426, Provisional US 2001-277469P 20010321, US 2001-842547 20010426
FDT AU 2001050221 A Based on WO 200180890

PRAI US 2001-277469P 20010321; US 2000-199757P 20000426; US 2001-842547 20010426

TI Use of nitric oxide mimetics for **inhibiting** or **preventing** a **malignant** cell phenotype, useful for **preventing**, monitoring or treating **cancer**.

AB WO 200180890 A UPAB: 20020208

NOVELTY - A novel method for **inhibiting** and **preventing** a **malignant** cell phenotype comprises administering to cells a low dose of a nitric oxide (NO) mimetic.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a method for increasing efficacy of an antimalignant therapeutic modality against **cancer** cells comprising administering to the cells a low dose of a NO mimetic;

(2) a formulation for **inhibiting** and **preventing** a **malignant** cell phenotype comprising a NO mimetic to increase, restore or maintain NO mimetic activity of cells to a level which **prevents** or **inhibits** a **malignant** cell phenotype;

(3) a method of treating **cancer** in a subject comprising administering a low dose of a NO mimetic;

(4) a method of monitoring or diagnosing the progression of a **tumor** in a patient comprising measuring a level of a **tumor** marker in a patient in the presence of a low dose of a NO mimetic;

(5) a method for decreasing a **tumor** marker level in a patient comprising administering to a patient a low dose of a NO mimetic;

(6) the use of a NO mimetic for preparation of a medicament for increasing, restoring, or maintaining NO mimetic activity of cells to a level which increases efficacy of an antimalignant therapeutic modality against **cancer** cells;

(7) the use of a NO mimetic for preparation of a medicament for increasing, restoring or maintaining NO mimetic activity of cells to a level which **inhibits** and **prevents** a **malignant** cell phenotype in an animal; and

(8) the use of a NO mimetic for preparation of a medicament for increasing, restoring or maintaining NO mimetic activity of cells to a level which **prophylactically inhibits** and **prevents** a **malignant** cell phenotype in an animal at high risk for developing **cancer**.

ACTIVITY - Cytostatic. The ability of an NO mimetic to **reduce** **cancer** progression in humans was demonstrated. In this study continuous transdermal patches were used to deliver very low doses of **GTN** (0.033mg/hour) to patients with recurrent prostatic adenocarcinoma. Patients with prostatic adenocarcinoma were selected for this study because the progression of this type of **cancer** correlates well with the plasma levels of prostate-specific antigen (PSA). Thus, the outcome of low dose NO mimetic therapy can be easily assessed by measuring PSA levels. Analysis of data from 2 patients in this study revealed a sharp decline in plasma PSA levels within 2 months of **GTN** treatment, thus indicating low dose NO mimetic therapy to he an effective approach to the management of **cancer**, particularly prostate **cancer** in humans.

MECHANISM OF ACTION - NO agonist. In in vitro invasion assays, either breast **cancer** cells or HTR-8/SVneo invasive trophoblasts were plated on MATRIGEL-coated membranes. Cells were then incubated under hypoxic or normal conditions, alone or in the presence of NO mimetics. The invasion index for each treatment was determined by staining the cells which invaded through the membrane and counting them. In both cell lines, treatment with low doses of NO mimetics significantly **reduced** hypoxic cell invasiveness as compared to untreated hypoxic cells. The invasive indices of hypoxic breast **cancer** cells treated with 10-10M SNP and 10-10M **GTN** were similar to or even lower than cells cultured under non-hypoxic conditions. In HTR-8/SVneo trophoblast cells, 10-7M **GTN** **inhibited** invasiveness of hypoxic cells by 56.2%, while 10-8M SNP **inhibited** invasiveness by 63.4%.

USE - Administration of the NO mimetics are useful in controlling **cancer** by **reducing** its growth and improving response to therapy, e.g. the methods and formulations can **inhibit** metastasis, invasiveness and progression of cells exhibiting a **malignant** phenotype. In addition, the methods and formulations can induce or maintain dormancy of cells exhibiting a **malignant** phenotype at primary as well as secondary sites of **tumors**. Further, these methods and formulations can **prevent** or decrease development of resistance of cells exhibiting a **malignant** cell phenotype to antimalignant therapeutic modalities as well as increase the efficacy of antimalignant therapeutic modalities. The methods may be used where the subject is at risk or suffering from a **malignant** cell phenotype, or to **inhibit** metastases and development of resistance to antimalignant therapeutic modalities in the cells (claimed). They can also be used to **inhibit** development of a more aggressive **malignant** cell phenotype in the cells upon administration of an anti-VEGF agent, or **inhibits** development of a **malignant** cell phenotype in cells exposed to factors which lower cellular NO mimetic activity, or to delay or reduce development of drug tolerance to the NO mimetic or side effects (claimed). The methods can be used for treating **cancer** such as prostate **cancer** (claimed). They can also be used for gastrointestinal **cancer**, testicular **cancer** and breast **cancer**, in diagnosing and monitoring a **malignant** cell phenotype in an animal via detection of levels of one or more markers indicative of a **malignant** cell phenotype following administration of a low dose of a NO mimetic. No change, a decrease or deceleration in the increase of the level of one or more of these markers in an animal following administration of a low dose NO mimetic as compared to the level of the marker in the animal prior to administration of the low dose NO mimetic is indicative of a **malignant** cell phenotype in the animal.

Dwg.0/3

TECH UPTX: 20020208

TECHNOLOGY FOCUS - PHARMACEUTICALS - The NO mimetic may include an NO donor and a compound that **inhibits** cyclic nucleotide degradation. The NO mimetics may be **nitroglycerin** (**GTN**), isosorbide 5-mononitrate (ISMN), isosorbide dinitrate (ISDN), pentaerythritol tetranitrate (PETN), erthrityl tetranitrate (ETN), amino acid derivatives e.g. N-hydroxyl-L-arginine (NOHA), N6-(1-iminoethyl)lysine) (L-NIL), L-N-e5-(1-iminoethyl)ornithine (LN-NIO), Nomega-methyl-L-arginine (L-NMMA), and S-nitrosoglutathione (SNOG); and other compounds which generate or release NO under physiologic conditions e.g. S,S-dinitrosodithiol (SSDD), (N-(2-(nitroxyethyl))-3-pyridinecarboxamide (nicorandil), sodium nitroprusside (SNP), S-nitroso-N-acetylpenicilamine (SNAP), 3-morpholino-sydnonimine (SIN-1), molsidomine, DEA-NONOate (2-(N,N-diethylamino)-diazenolate-2-oxide), and spermine NONOate (N-(4-(1-(3-aminopropyl)-2-hydroxy-2-nitrosohydrazino)butyl-1,3-propanediamine).

TT TT: NITRIC OXIDE **INHIBIT PREVENT MALIGNANT** CELL PHENOTYPE USEFUL **PREVENT** MONITOR TREAT **CANCER**

.

L9 ANSWER 4 OF 22 WPIDS (C) 2002 THOMSON DERWENT

AN 2001-267498 [28] WPIDS

DNC C2001-081170

TI Composition useful for delivery of drugs or cosmetic agents includes an epidermal permeation enhancer comprising monoacyl lysophospholipids.

DC B05 D21

IN BISHOP, M; GILLIS, G; NORTON, S J

PA (ACTI-N) ACTIVE ORGANICS INC

CYC 27

PI EP 1080719 A2 20010307 (200128)* EN 24p

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

JP 2002128702 A 20020509 (200234) 18p
KR 2002018566 A 20020308 (200262)
ADT EP 1080719 A2 EP 2000-118980 20000901; JP 2002128702 A JP 2001-262591 20010831; KR 2002018566 A KR 2001-52644 20010830
PRAI US 2000-654421 20000901; US 1999-152305P 19990903
TECH UPTX: 20010522
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Active Ingredients: These are drugs that act on epidermal or subepidermal layers, especially: steroid hormones, e.g. progesterone, estrogen, testosterone or their derivatives; peptide hormones, e.g. melatonin, AGHA, IGF, interleukins, interferons, MSH, a-TGF, b-TGF, TNF or MCH; lipid hormones, e.g. platelet-derived growth factor, retinoic acid, leukotrienes or prostaglandins; or nucleic acid based polymers. The drug may be an analgesic (especially acetylsalicyclic acid. ibuprofen, acetaminophen, capsaicin, menthol, and methyl salicylate); for treating arthritis; for inducing vasodilation (especially sildenafil, arginine and compounds effecting the levels and action of nitric oxide); for treating addiction (especially nicotine); for depression (e.g. naltrexone, valium, serotonin uptake **inhibitors**); for treating **cancer**; heart disease (e.g. **nitroglycerine**); bacterial infections (e.g. penicillins, tetracyclines); viral infections (e.g. AZT, interferon); parasitic infestations (especially ivermectin); fungal infections; antioxidants (e.g. propyl gallate); and also agents acting as oxygen deliverers, for diminishing hyperpigmentation, exfoliants, as a superficial, medium depth or deep skin peel, astringents, humectants, drugs acting as isoflavones (e.g. genisten, glycetein), drugs acting as terpenoids, drugs acting as vitamins and a wide range of specified substances useful as cosmetic actives.

L9 ANSWER 5 OF 22 MEDLINE DUPLICATE 2
AN 2002003696 MEDLINE
DN 21623993 PubMed ID: 11752013
TI Nitric oxide-mediated regulation of chemosensitivity in cancer cells.
AU Matthews N E; Adams M A; Maxwell L R; Gofton T E; Graham C H
CS Department of Anatomy and Cell Biology, Queen's University, Kingston, ON, Canada.
SO JOURNAL OF THE NATIONAL CANCER INSTITUTE, (2001 Dec 19) 93 (24) 1879-85. Journal code: 7503089. ISSN: 0027-8874.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200201
ED Entered STN: 20020102
Last Updated on STN: 20020128
Entered Medline: 20020123
AB BACKGROUND: Hypoxia in **tumors** is associated with **malignant** progression, metastatic spread, and increased resistance to radiotherapy and chemotherapy. Molecular O(2) is required for the cellular production of nitric oxide (NO) by the enzyme NO synthase (NOS), and NO may block components of the adaptive response to hypoxia. Hence, we hypothesized that hypoxia increases drug resistance in **tumor** cells by **inhibiting** endogenous NO production. METHODS: Human breast carcinoma (MDA-MB-231) and mouse melanoma (B16F10) cells were pre-exposed to 20% O(2), 5% O(2), or 1% O(2), incubated with a pharmacologic inhibitor of endogenous NO production, and then treated with chemotherapeutic agents. Resistance was assessed by colony-formation assays, and western blot analysis was used to measure NOS protein levels. All P values were two-sided. RESULTS: Incubation of MDA-MB-231 **tumor** cells in 1% O(2) maximally increased their resistance to doxorubicin and 5-fluorouracil by 8.5-fold (P =.002) and 2.3-fold (P =.002), respectively, compared with incubation in 20% O(2). B16F10 mouse melanoma cells preincubated in 1% O(2) (versus 20% O(2)) for 12 hours exhibited a twofold increase in resistance to doxorubicin (P<.001). The

rapid acquisition of drug resistance after exposure to 1% O(2) could be mimicked by incubating the MDA-MB-231 cells for 12 hours with the NOS **inhibitor** N(G)-monomethyl-Larginine (fivefold increase; P<.001). Conversely, replacement of NO activity by use of the NO-mimetic **glyceryl trinitrate** (**GTN**) and diethylenetriamine NO adduct produced statistically significant attenuations in the development of resistance of 59% (P<.001) and 40% (P<.001), respectively, in MDA-MB-231 cells. Treatment of B16F10 cells with **GTN** produced a 58% **reduction** in resistance (P<.001). MDA-MB-231 cells expressed all three isoforms of the NOS enzyme at levels that were not altered by exposure to hypoxia. CONCLUSIONS: NO mediates chemosensitivity in **tumor** cells, and hypoxia-induced drug resistance appears to result, in part, from downstream suppression of endogenous NO production. These results raise the possibility that administration of small doses of NO mimetics could be used as an adjuvant in chemotherapy.

L9 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
AN 2001:580985 CAPLUS
DN 135:327073
TI **Nitroglycerin**: a NO donor **inhibits** TPA-mediated **tumor** promotion in murine skin
AU Trikha, Prashant; Sharma, Nidhi; Athar, M.
CS Department of Medical Elementology and Toxicology, Hamdard University, New Delhi, 110 062, India
SO Carcinogenesis (2001), 22(8), 1207-1211
CODEN: CRNGDP; ISSN: 0143-3334
PB Oxford University Press
DT Journal
LA English
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI **Nitroglycerin**: a NO donor **inhibits** TPA-mediated **tumor** promotion in murine skin
AB **Nitroglycerin** (**GTN**), a nitric oxide (NO) generating vasodilator has been used in the present study to assess the role of NO during **tumor** promotion in murine skin. Administration of **GTN** to 12-O tetradecanoyl phorbol 13-acetate (TPA)-treated mice resulted in a dose-dependent **inhibition** in the level of glutathione and the activity of antioxidant enzymes by .apprx.16-40% of acetone-treated control. We also obsd. that **GTN** application led to a significant redn. in the ornithine decarboxylase (ODC) activity and decreased the rate of [3H]thymidine incorporation into epidermal DNA when compared with the acetone-treated control (P < 0.001). Treatment of DMBA-initiated TPA-promoted mice with **GTN** increased the latency period, decreased the **tumor** incidence by 32% and there was a 2-fold decrease in **tumor** yield (**tumor**/mouse) as compared with the TPA (alone)-treated group by 20 wk. From these data, it can be concluded that NO can abrogate the toxic and **tumor** promoting effects of TPA and **GTN** can be used as a chemopreventive agent to **inhibit tumorigenesis** in murine skin.
ST **tumor** promotion **inhibitor** NO donor **nitroglycerin** TPA skin
IT DNA formation
(**nitroglycerin**, a NO donor **inhibits** TPA-mediated **tumor** promotion in murine skin)
IT **Antitumor** agents
(promotion **inhibitors**; **nitroglycerin**, a NO donor **inhibits** TPA-mediated **tumor** promotion in murine skin)
IT **55-63-0**, **Nitroglycerin** 10102-43-9, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(**nitroglycerin**, a NO donor **inhibits** TPA-mediated **tumor** promotion in murine skin)

IT 70-18-8, Glutathione, biological studies 9001-05-2, Catalase 9001-48-3, Glutathione **reductase** 9013-66-5, Glutathione peroxidase 9024-60-6, Ornithine decarboxylase 50812-37-8, Glutathione S-transferase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**nitroglycerin**, a NO donor **inhibits** TPA-mediated **tumor** promotion in murine skin)

L9 ANSWER 7 OF 22 MEDLINE
AN 2002087871 MEDLINE
DN 21674687 PubMed ID: 11815745
TI [Sevoflurane in stop-flow interventions. Hemodynamics study]. Sevoflurano per interventi di "stop-flow". Uno studio emodinamico.
AU Di Filippo A; Marini F; Barneschi M G; Falchi S; Novelli G P
CS Dipartimento Area Critica Medico-chirurgica, Sezione di Anestesia e Rianimazione, Universita degli Studi, Firenze, Italy.
SO MINERVA ANESTESIOLOGICA, (2001 Dec) 67 (12) 849-53.
Journal code: 0375272. ISSN: 0375-9393.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
LA Italian
FS Priority Journals
EM 200210
ED Entered STN: 20020130
Last Updated on STN: 20021002
Entered Medline: 20021001
AB BACKGROUND: The so called stop-flow operation is based on locoregional perfusion with an antiblastic hypoxic solution of the region invaded by **malignant** tissue. Cardiocirculatory complications are common, mainly consisting of **reduction** of cardiac index, increase of arterial pulmonary pressure, systemic vascular resistance and heart rate. Sevoflurane has been used for its stable hemodynamic profile to **reduce** cardiocirculatory troubles. METHODS: Six patients were submitted to stop-flow operation. General anaesthesia was performed with Sevoflurane 1 MAC in Air/O2. The following parameters were recorded: **nitroglycerin** infusion m order to maintain the position of the balloon of the catheters, arterial oxygen saturation, end-tidal carbon dioxide, mean arterial pressure, central venous pressure, arterial pulmonary pressure, heart rate and mixed oxygen venous saturation; recordings were performed before stop-flow (T1), during stop-flow (T2) and 10' after reperfusion (T3). RESULTS: Before stop-flow (T1) all the parameters were normal. At T2 heart rate, cardiac index and pulmonary capillary wedge pressure increased whilst mean arterial pressure, systemic vascular resistance and pulmonary vascular resistance decreased. Ten minutes after the end of perfusion (T3) absence of variations in systemic vascular resistance, in pulmonary vascular resistance, in pulmonary capillary wedge pressure, in cardiac index and in mixed oxygen venous saturation were noticed. Heart rate and central venous pressure showed a tendency to decrease. CONCLUSIONS: The hemodynamic profile during stop-flow appears to be stable with general anaesthesia with Sevoflurane.

L9 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2002 ACS
AN 2000:839294 CAPLUS
DN 133:355227
TI Medicinal composition for preventing and treating high intracranial pressure
IN Xu, Shaoheng
PA He, Guangxue, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 5 pp.
CODEN: CNXXEV

DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1250651	A	20000419	CN 1998-120141	19981009

AB The title compn. [injection] for preventing and treating high intracranial pressure due to e.g. brain trauma, brain **tumor** or cerebrovascular disease is composed of piracetam in 0.85- 0.9% NaCl soln. The injection may also contain mannitol, beta-escin sodium, **glycerol trinitrate**, and/or Na nitroprusside.

IT Brain, **neoplasm**
(medicinal compn. for **preventing** and treating high intracranial pressure)

IT 55-63-0, Glycerol **trinitrate** 69-65-8, Mannitol 7491-74-9, Piracetam 14402-89-2, Sodium nitroprusside 64156-26-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medicinal compn. for **preventing** and treating high intracranial pressure)

L9 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4
AN 2000:684926 CAPLUS
DN 134:85443
TI Effect of dietary vitamin e on spontaneous or nitric oxide donor-induced mutations in a mouse tumor model
AU Sandhu, Jagdeep K.; Haqqani, Arsalan S.; Birnboim, H. Chaim
CS Department of Biochemistry, Microbiology, and Immunology Ottawa Regional Cancer Centre, University of Ottawa, Ottawa, ON, K1H 8L6, Can.
SO Journal of the National Cancer Institute (2000), 92(17), 1429-1433
CODEN: JNCIEQ; ISSN: 0027-8874
PB Oxford University Press
DT Journal
LA English
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Vitamin E, an antioxidant, has been investigated for its effect on **cancer** incidence in humans, but no firm conclusions about a protective effect can be drawn from these studies. Recently, we reported a statistically significant correlation in the Mutatect mouse **tumor** model between the no. of neutrophils and the frequency of mutation at the hypoxanthine phosphoribosyltransferase (hprt) locus. We have now used this model to investigate vitamin E's effect on the hprt mutation rate. Mutatect cells were grown in mice as s.c. **tumors** for 2-3 wk, the **tumor** cells were recovered, and 6-thioguanine-resistant (i.e., hprt mutant) colonies were scored. Myeloperoxidase activity was used as a measure of neutrophil infiltration. Vitamin E (2 IU/kg body wt.) was provided in the diet for 3-4 wk. In some expts., **glyceryl trinitrate** (100 mg/kg body wt.) was also administered as a source of nitric oxide. All statistical tests were two-sided. Mouse **tumors** from the Mutatect MN-11 cell line exhibited a 3.2-fold higher median mutation frequency than the same cells in culture ($P<.0001$); vitamin E reduced this frequency by 24.9% ($P=.01$). Mutatect TM-28-derived **tumors** (which secrete interleukin 8) were heavily infiltrated with neutrophils and had a correspondingly high mutation frequency; in two sep. expts., vitamin E reduced the median mutation frequency by 68.9% ($P = .0019$) and 84.1% ($P = .011$) and myeloperoxidase levels by 75.3% ($P = .0002$) and 75.5% ($P = .026$), resp. **Glyceryl trinitrate** increased the mutation frequency in MN-11 **tumors**, and vitamin E **reduced** the median frequency by 61.4% ($P = .058$). Dietary vitamin E afforded strong protection against both spontaneously arising and nitric oxide induced mutations. Two sep. protective mechanisms by vitamin E may be operating: scavenging of a nitric oxide-related genotoxic species and altering the infiltration of neutrophils into **tumors**.

L9 ANSWER 10 OF 22 MEDLINE
AN 2001260463 MEDLINE
DN 21187793 PubMed ID: 11291271
TI [Drug therapy of hemorrhage in esophageal and gastric varices: role of vasoactive drugs].
Medikamentna terapija krvarenja iz varikoziteta jednjaka i zeluca: mjesto i uloga vazoaktivnih lijekova.
AU Pulanic R
CS Referentni centar Ministarstva zdravstva Republike Hrvatske za intervencijsku gastroenterologiju, Zavod za gastroenterologiju, Interna klinika Rebro, Zagreb.
SO LIJECNICKI VJESNIK, (2000 Nov-Dec) 122 (11-12) 276-83.
Journal code: 0074253. ISSN: 0024-3477.
CY Croatia
DT Journal; Article; (JOURNAL ARTICLE)
LA Serbo-Croatian
FS Priority Journals
EM 200105
ED Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517
AB Esophageal and gastric variceal bleeding is one of the most severe complications of portal hypertension and with high mortality. The aim of the therapy is to stop bleeding, replace the lost amount of blood and erythrocytes, treat coagulopathy, prevent rebleeding and improve liver function. Commonly accepted method to stop bleeding from varices is endoscopic hemostasis. Four vasoactive drugs, two natural peptides (vasopressin and somatostatin) and their analogues (terlipressin and octreotide) can control acute bleeding from gastric and esophageal varices. They lower portal pressure and the pressure in colateral circulation by vasoconstriction in splanchnic basin, and by **inhibition** the activity of endogenous vasodilatators. The high incidence of serious side-effects of vasopressin, even with **nitroglycerin**, has limited its application and decreased the use of this drug, with its abandonment in Europe. The vasopressin analogue, terlipressin, has a lower number of side-effects and is more effective in control of bleeding. Early terlipressin application at home, prior to hospital admission, diminishes mortality due to bleeding, thus attaching additional importance to this drug. Somatostatin, when applied as intravenous bolus injection, controls acute bleeding very efficiently and quickly. Five day somatostatin infusion after endoscopic hemostasis prevents rebleeding, with minimal side-effects. Octreotide is very efficient in long-term therapy of endocrine **tumors** due to its longer half-life, better hormone **inhibition**, and simple application compared to somatostatin. Like somatostatin, it can also control variceal bleeding. It appears that the long-term subcutaneous octreotide application prevents rebleeding and improves liver function, all of which yields a new dimension to its use.

L9 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5
AN 2000:559163 CAPLUS
DN 133:359022
TI Cardiopulmonary bypass exacerbates oxidative stress but does not increase proinflammatory cytokine release in patients with diabetes compared with patients without diabetes: Regulatory effects of exogenous nitric oxide
AU Matata, Bashir M.; Galinanes, Manuel
CS Division of Cardiac Surgery, Glenfield Hospital, University of Leicester, Leicester, UK
SO Journal of Thoracic and Cardiovascular Surgery (2000), 120(1), 1-11
CODEN: JTCSAQ; ISSN: 0022-5223
PB Mosby, Inc.
DT Journal
LA English

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Cardiopulmonary bypass induces oxidative stress and a whole-body inflammatory reaction that are believed to increase surgical morbidity. Our goal was to investigate the effect of nitric oxide supplementation on bypass-induced oxidative stress and inflammatory reaction in patients with and without diabetes undergoing elective coronary bypass graft surgery. Patients with and without diabetes were randomized to receive an infusion of saline soln. or the nitric oxide donor **nitroglycerin** at 1 .mu.g .cntdot. kg-1 .cntdot. min-1 starting 10 min before the initiation of cardiopulmonary bypass and then maintained for 4 h (n = 10 per group). Serial blood samples were taken at various intervals and plasma was analyzed for makers of oxidative stress (lipid hydroperoxides, protein carbonyls, and protein nitrotyrosine) and inflammation (complement C3a, elastase, interleukin 8, and **tumor** necrosis factor .alpha.). Cardiopulmonary bypass significantly increased lipid hydroperoxides, protein carbonyls, protein nitrotyrosine, complement C3a, elastase, sol. E-selectin, interleukin 8, and **tumor** necrosis factor .alpha. in both groups. Infusion of **nitroglycerin** significantly **reduced** the increase in lipid hydroperoxides and protein carbonyls in patients who have diabetes without affecting levels in patients without diabetes. **Nitroglycerin** infusion markedly **reduced** protein nitrotyrosine and **tumor** necrosis factor .alpha. levels in both groups. In contrast, **nitroglycerin** infusion significantly increased C3a in patients without diabetes and increased elastase and interleukin 8 levels in patients with diabetes. Cardiopulmonary bypass induces a greater oxidative stress in patients with diabetes than in those without diabetes, and the inflammatory reaction is qual. different in the 2 groups of patients. In addn., **nitroglycerin reduces** oxidative stress in patients with diabetes and differentially affects the inflammatory response to bypass both in patients with and in those without diabetes. The results have important implications with respect to the use of nitric oxide donors during cardiopulmonary bypass.

L9 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
AN 1999:515031 CAPLUS
DN 131:281008
TI Effect of oligomer length and base substitutions on the cytotoxic activity and specific nuclear protein recognition of GTn oligonucleotides in the human leukemic ccrf-cem cell line.
AU Morassutti, Carla; Dapas, Barbara; Scaggiante, Bruna; Paroni, Gabriela; Xodo, Luigi; Quadrifoglio, Franco
CS Department of Biomedical Sciences and Technologies, University of Udine, Udine, 33100, Italy
SO Nucleosides & Nucleotides (1999), 18(6 & 7), 1711-1716
CODEN: NUNUD5; ISSN: 0732-8311
PB Marcel Dekker, Inc.
DT Journal
LA English
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB We have identified phosphodiester oligonucleotides composed of G and T bases, named **GTn**, which are able to **inhibit** the cellular growth of human **cancer** cell lines by recognizing specific nuclear proteins. We demonstrated that **GTn** oligonucleotides require a length of at least 20 nucleotides to exert a significant cytotoxic effect and to retain the specific protein binding ability. In addn., we found that **GTn** cytotoxicity was lost when A or C bases were introduced at either 3' and 5' end or within the **GTn** sequences.

IT Structure-activity relationship
(leukemia-**inhibiting**; effect of oligomer length and base substitutions on the cytotoxic activity and specific nuclear protein

recognition of **GTn** oligonucleotides in the human leukemic ccrf-cem cell line.)

IT **Antitumor** agents
(leukemia; effect of oligomer length and base substitutions on the cytotoxic activity and specific nuclear protein recognition of **GTn** oligonucleotides in the human leukemic ccrf-cem cell line.)

L9 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 7
AN 2000:55762 CAPLUS
DN 132:260163
TI Effect of phosphorothioate modifications on the ability of **GTn** oligodeoxynucleotides to specifically recognize single-stranded DNA-binding proteins and to affect human **cancer** cellular growth
AU Morassutti, Carla; Scaggiante, Bruna; Dapas, Barbara; Xodo, Luigi; Tell, Gianluca; Quadrifoglio, Franco
CS Department of Biomedical Sciences & Technologies and Department of Bone Marrow Transplant, School of Medicine, University of Udine, Udine, 33100, Italy
SO Biochimie (1999), 81(12), 1115-1122
CODEN: BICMBE; ISSN: 0300-9084
PB Editions Scientifiques et Medicales Elsevier
DT Journal
LA English
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Effect of phosphorothioate modifications on the ability of **GTn** oligodeoxynucleotides to specifically recognize single-stranded DNA-binding proteins and to affect human **cancer** cellular growth
AB We have previously identified phosphodiester oligonucleotides exclusively made of G and T bases, named **GTn**, that significantly **inhibit** human **cancer** cell growth and recognize specific nuclear single-stranded DNA binding proteins. We wished to examine the ability of the modified **GTn** oligonucleotides with different degrees of phosphorothioate modifications to bind specifically to the same nuclear proteins recognized by the **GTn** phosphodiester analogs and their cytotoxic effect on the human T-lymphoblastic CCRF-CEM cell line. We showed that the full phosphorothioate **GTn** oligonucleotide was neither able to specifically recognize those nuclear proteins, nor cytotoxic. In contrast, the 3'-phosphorothioate-protected **GTn** oligonucleotides can maintain the specific protein-binding activity. The end-modified phosphorothioate oligonucleotides were also able to elicit the dose-dependent cell growth inhibition effect, but a loss in the cytotoxic ability was obsd. increasing the extent of sulfur modification of the sequences. Our results indicate that phosphorothioate oligonucleotides directed at specific single-stranded DNA-binding proteins should contain a no. of phosphorothioate end-linkages which should be related to the length of the sequence, in order to maintain the same biol. activities exerted by their phosphodiester analogs.
IT Structure-activity relationship
(**antitumor**; effect of phosphorothioate modifications on ability of **GTn** oligodeoxynucleotides to specifically recognize single-stranded DNA-binding proteins and to affect human **cancer** cellular growth)
IT **Antitumor** agents
(effect of phosphorothioate modifications on ability of **GTn** oligodeoxynucleotides to specifically recognize single-stranded DNA-binding proteins and to affect human **cancer** cellular growth)
IT Phosphorothioate oligodeoxyribonucleotides
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(effect of phosphorothioate modifications on ability of **GTn** oligodeoxynucleotides to specifically recognize single-stranded

DNA-binding proteins and to affect human **cancer** cellular growth)

IT 9026-81-7, Nuclease
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(degrdn. by; effect of phosphorothioate modifications on ability of **GTn** oligodeoxynucleotides to specifically recognize single-stranded DNA-binding proteins and to affect human **cancer** cellular growth)

IT 191942-18-4 206011-37-2 260960-66-5 261151-40-0 261151-41-1 262946-50-9 262946-51-0 262946-52-1
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(effect of phosphorothioate modifications on ability of **GTn** oligodeoxynucleotides to specifically recognize single-stranded DNA-binding proteins and to affect human **cancer** cellular growth)

L9 ANSWER 14 OF 22 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 8
AN 1998:168188 CAPLUS
DN 128:289833
TI Human **cancer** cell lines growth **inhibition** by **GTn** oligodeoxyribonucleotides recognizing single-stranded DNA-binding proteins
AU Scaggiante, Bruna; Morassutti, Carla; Dapas, Barbara; Tolazzi, Giuseppe; Ustulin, Franca; Quadrifoglio, Franco
CS Department of Biomedical Sciences and Technologies and Department of Bone Marrow Transplant, University of Udine, Udine, I-33100, Italy
SO European Journal of Biochemistry (1998), 252(2), 207-215
CODEN: EJBCAI; ISSN: 0014-2956
PB Springer-Verlag
DT Journal
LA English
TI Human **cancer** cell lines growth **inhibition** by **GTn** oligodeoxyribonucleotides recognizing single-stranded DNA-binding proteins
AB Oligonucleotides can specifically target not only nucleic acids but also proteins. Some proteins recognizing oligonucleotides in a sequence-specific manner have been related to **cancer** transformation and progression. We have found that oligonucleotides composed by repeated and/or variable intervals of **GTn** with 1 .ltoreq. n .ltoreq. 7, are able to exert a specific and dose-dependent growth **inhibition** on human CCRF-CEM, CEM-VLB300, U937, Jurkat, H9 and HeLa **tumor** cell lines. In contrast, G.fwdarw.C, G.fwdarw.A, T.fwdarw.C and T.fwdarw.A base substituted control oligonucleotides do not significantly alter cellular growth. In all cell lines, a nuclear protein (mol. mass = 45.+-.7 kDa), which specifically recognizes **GTn**, was identified. Our hypothesis is that the formation of the **GTn**-protein complex in human **cancer** cell lines may be involved in the growth **inhibition** effect. In fact, we found that the redn. or lack of cytotoxic effects by **GTn** in phorbol 12-myristate 13-acetate-treated CCRF-CEM cells and in normal human lymphocytes is paralleled by the simultaneous redn. or lack of **GTn**-protein complex. Oligonucleotides specifically "quenching" intracellular protein activities by forming oligonucleotide-protein complexes may be of potential interest in the treatment of human **tumors**.
ST oligodeoxyribonucleotide **cancer inhibition** protein target
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SSB (single-stranded DNA-binding); human **cancer** cell lines

growth **inhibition** by **GTn** oligodeoxyribonucleotides recognizing single-stranded DNA-binding proteins)

IT **Antitumor** agents
(human **cancer** cell lines growth **inhibition** by **GTn** oligodeoxyribonucleotides recognizing single-stranded DNA-binding proteins)

IT Oligodeoxyribonucleotides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(human **cancer** cell lines growth **inhibition** by **GTn** oligodeoxyribonucleotides recognizing single-stranded DNA-binding proteins)

IT 191942-17-3 191942-18-4 191942-19-5 191942-20-8 191942-21-9
191942-22-0 206011-33-8 206011-34-9 206011-35-0 206011-36-1
206011-37-2 206011-38-3 206011-39-4 206011-40-7 206011-41-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(human **cancer** cell lines growth **inhibition** by **GTn** oligodeoxyribonucleotides recognizing single-stranded DNA-binding proteins)

L9 ANSWER 15 OF 22 CAPLUS COPYRIGHT 2002 ACS
AN 1996:421105 CAPLUS
DN 125:104480
TI Transferrin dependence of Ga (NO3)3 **inhibition** of growth in human-derived small cell lung **cancer** cells
AU Weiner, Ronald E.; Avis, Ingallil; Neumann, Ronald D.; Mulshine, James L.
CS Nuclear Medicine Department, University Connecticut Health Center, Farmington, CT, 06030, USA
SO Journal of Cellular Biochemistry (1996), (Suppl. 24, NCI-Navy Medical Oncology Branch Cell Line Supplement), 276-287
CODEN: JCEBD5; ISSN: 0730-2312
PB Wiley-Liss
DT Journal
LA English
TI Transferrin dependence of Ga (NO3)3 **inhibition** of growth in human-derived small cell lung **cancer** cells
AB The effect of a combination of anti-transferrin receptor (TFR) antibody, 42/6, and Ga(NO3)3 on cell growth was examd. in small cell lung **cancer** (SCLC) cell lines: classic, NCI-H209, NCI-H345, NCI-H510; and variant, NCI-H82 and NCI-N417. The role of TFR and transferrin (TF) in Ga(NO3)3 cellular uptake was also tested. Exogenous TF did not enhance the cytotoxicity of Ga. At >3 .mu.g/mL, Ga(NO3)3 inhibited growth in all cell lines in TF-supplemented or deficient media. At <3 .mu.g/mL, Ga stimulated growth for all cells but this effect was eliminated by TF or 42/6. Classic SCLC lines required 3-4 fold less exogenous gallium than variant lines to reduce cell no. by 50%. The mean Ga uptake (**ng** /106 cells) in H345 and H209 cell lines was 4-5-fold compared to H82 and N417 uptake ($P < 0.001$). The 42/6 reduced exogenous TF-stimulated growth. Antibody plus Ga(NO3)3 caused a slight further cell no. decline in all cell lines in TF-supplemented or deficient media. These results suggest that the addn. of 42/6 antibody treatment would not increase the effectiveness of Ga(NO3)3 in patients. Both exogenous and endogenous TF and TFR play an important role in Ga uptake in these cells.

IT Biological transport
(transferrin dependence of gallium nitrate **inhibition** of growth in human-derived small-cell lung **cancer** cells)

IT Transferrin receptors
Transferrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transferrin dependence of gallium nitrate **inhibition** of growth in human-derived small-cell lung **cancer** cells)

IT **Neoplasm inhibitors**

(lung small-cell carcinoma, transferrin dependence of gallium nitrate **inhibition** of growth in human-derived small-cell lung **cancer** cells)

IT Lung, **neoplasm**
(small-cell carcinoma, **inhibitors**, transferrin dependence of gallium nitrate **inhibition** of growth in human-derived small-cell lung **cancer** cells)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transferrin, transferrin dependence of gallium nitrate **inhibition** of growth in human-derived small-cell lung **cancer** cells)

IT 13494-90-1, Gallium **trinitrate**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(transferrin dependence of gallium nitrate **inhibition** of growth in human-derived small-cell lung **cancer** cells)

L9 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 9
AN 1995:902368 CAPLUS
TI Various cells release a stable small molecule that inhibits endothelium-dependent relaxation
AU Liu, James J.; Xie, Bing; Thurlow, Peter J.; Wiley, James S.; Chen, Joan R.
CS Vascular Biol. Unit, Univ. Melbourne, Heidelberg, Victoria, 3084, Australia
SO Am. J. Physiol. (1995), 269(4, Pt. 2), H1303-H1311
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB Previous studies have shown that neutrophils release a stable factor that inhibits endothelium-dependent relaxation. In the present studies, the effects of supernatants derived from various cells on endothelium-dependent relaxation were studied. Cells were obtained from seven sources: human hematopoietic cells including mononuclear leukocytes (MONO), polymorphonuclear leukocytes (PMNs), and chronic lymphocytic leukemia (CLL) cells; cells of the cardiovascular system including human endothelial cell line ECV304, human smooth muscle cells, and rat myocardial cells; and the **tumor** cell line HPB. These isolated or cultured cells were incubated for 1 h in Krebs soln. to release the factor. The results shwoed that the supernatants from 105 cells/mL of all cells except the **tumor** cell line HPB produced a potent **inhibitory** effect on endothelium-dependent relaxation of rat aortic rings in response to acetylcholine and Ca2+ ionophores A23187 and ionomycin but not on endothelium-independent relaxation to nitroprusside and **glyceryl trinitrate**. When the concn. increased to 106 cell/mL, the supernatants from the **tumor** cell line HPB also slightly but significantly **inhibited** endothelium-dependent relaxation. The potency order was PMNs = MONO = CLL cells > cardiac cells > smooth muscle cells > the endothelial cell line ECV304 > the **tumor** cell line HPB. It seems that the hematopoietic cells and the cardiac cells are more active in release of the factor. The effect of this factor was rapid in onset and hard to wash out. A cycloxygenase inhibitor or a thromboxane A2-prostaglandin H2 receptor antagonist partially but significantly reduced the effect of the factor. In contrast, 5-lipoxygenase inhibitors potentiated its effect. However, these agents did not inhibit the release of the factor from the cells. Chem. characterization showed that the factor was stable to heat, extreme pH an protease, and had a molecualr mass under 500 Da. In conclusion, a naturally occurring, stable, nonprotein, small, novel mol. produces a potent, rapid, long-lasting, inhibitory effect on endothelium-dependent

relaxation. Because it can be released from various cells, it may have functions beyond the inhibition of the vascualr relaxation.

L9 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 10
AN 1994:432959 CAPLUS
DN 121:32959
TI Nitric oxide involvement in tumor-induced immunosuppression
AU Lejeune, Pascale; Lagadec, Patricia; Onier, Nathalie; Pinard, Dominique; Ohshima, Hiroshi; Jeannin, Jean Francois
CS Fac. Med., Dijon, Fr.
SO Journal of Immunology (1994), 152(10), 5077-83
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
AB The mechanisms of immunosuppression induced by colon **cancer** in rats were investigated at the systemic and **tumor** levels. During **tumor** growth (after i.p. injection of rat colon adenocarcinoma cells in syngeneic BD IX rats), Con A-induced proliferation of splenic mononuclear cells decreased and nitric oxide (NO) prodn. by splenic macrophages increased concomitantly. Incubating splenic mononuclear cells with an inhibitor of NO synthase, **NG**-monomethyl-L-arginine, restored lymphocyte proliferation. A low level of inducible NO synthase mRNA was detectable in **tumors** by Northern blotting, with a weak increase during **tumor** growth. The NO concn. measured in the **tumor** nodules increased weakly in parallel to the **tumor** growth. Five and six weeks after **tumor** cell injection, **tumor**-infiltrating lymphocytes from disaggregated **tumors** did not proliferate in the presence of Con A. Addn. of **NG** -monomethyl-L-arginine **inhibited** the prodn. of NO in **tumor** dissocns. and enhanced **tumor**-infiltrating lymphocyte proliferation. **Glyceryl trinitrate** (a No-releasing compd.) totally **inhibited** the lymphocyte proliferation in vitro while it slightly **reduced** the **tumor** cell proliferation. T lymphocytes were therefore more sensitive to NO than were **tumor** cells. Culture medium from **tumor** cells induced NO prodn. by splenic macrophages, although the factor involved has not yet been identified. Furthermore, **tumor** cells could also play a part in NO prodn. by **tumors** because the **tumor** cells were induced to produce NO by IFN-.gamma. plus IL-1. These results strongly suggest the participation of NO in the **tumor**-induced immunosuppression in rats.

L9 ANSWER 18 OF 22 CAPLUS COPYRIGHT 2002 ACS
AN 1992:4477 CAPLUS
DN 116:4477
TI Human colorectal adenocarcinoma cells: differential nitric oxide synthesis determines their ability to aggregate platelets
AU Radomski, Marek W.; Jenkins, David C.; Holmes, Lesley; Moncada, Salvador
CS Wellcome Res. Lab., Beckenham/Kent, BR3 3BS, UK
SO Cancer Research (1991), 51(22), 6073-8
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB The existence and role of an L-arginine:nitric oxide (NO) pathway in two human colorectal adenocarcinoma cell lines, SW-480 and SW-620, were investigated. Both cell lines, which derive from the same patient, SW-480 from the primary **tumor** and SW-620 from its metastatic lesion, were shown to have a cytosolic, Ca2+-independent, NADPH-dependent NO synthase, the activity of which was lower in the cytosol of SW-620. These cells were more potent inducers of platelet aggregation. In contrast, SW-480, which had greater NO synthase activity, were less potent inducers of platelet aggregation. Pretreatment of both cell lines with **NG** -monomethyl-L-arginine, an inhibitor of NO synthase, potentiated their proaggregating effect and made them equally active. Exogenous L-arginine,

NO, and related nitrovasodilators all inhibited platelet aggregation induced by SW-620. The antiaggregating activity of NO was further potentiated by prostacyclin and by M&B22948, a selective inhibitor of cyclic GMP phosphodiesterase. The authors propose that the generation of NO by **tumor** cells inversely correlates with their metastatic potential. Furthermore, it is shown that the lower activity of NO synthase in metastatic cells is due to the presence in these cells of a low mol. wt. inhibitor of the NO synthase. In addn., agents which modulate platelet function by a cyclic GMP-dependent mechanism may be useful in the **prevention** of **tumor** metastasis.

IT 9068-52-4
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**, nitric oxide **inhibition** of **tumor** cell-induced blood platelet aggregation potentiation by)

IT 35121-78-9, Prostacyclin 37762-06-4
RL: BIOL (Biological study)
(nitric oxide **inhibition** of **tumor** cell-induced blood platelet aggregation potentiation by)

IT **55-63-0**, **Glyceryl trinitrate** 79032-48-7, S-Nitroso-N-acetylpenicillamine
RL: BIOL (Biological study)
(**tumor** cell-induced platelet aggregation **inhibition** by)

L9 ANSWER 19 OF 22 MEDLINE
AN 90355399 MEDLINE
DN 90355399 PubMed ID: 2388398
TI A case report of anesthesia for concomitant right pneumonectomy and coronary artery bypass operations.
AU Shibuya N; Satoh Y
CS Division of Anesthesia, Tachikawa General Hospital, Nagaoka.
SO MASUI. JAPANESE JOURNAL OF ANESTHESIOLOGY, (1990 Jun) 39 (6) 782-5. Journal code: 0413707. ISSN: 0021-4892.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 199009
ED Entered STN: 19901026
Last Updated on STN: 19901026
Entered Medline: 19900927
AB A 61-year-old man with previous myocardial infarction, was diagnosed as having lung **cancer**. Coronary arteriogram revealed stenoses of left anterior descending artery. We did the concomitant pulmonary and cardiac operations. Anesthesia was induced with fentanyl 1.5 mg and pancuronium 6 mg. A 37 Fr double-lumen endotracheal tube was inserted. Then a pulmonary artery catheter was inserted. The patient was given **nitroglycerin** for **prevention** of myocardial ischemia. The **tumor** had invaded pulmonary artery and therefore right pneumonectomy was necessary. After resection of right lung, coronary artery bypass operation was performed. On weaning from cardio-pulmonary bypass, pulmonary artery pressure increased to 48/20mmHg. Therefore he required dopamine and dobutamine each 4 micrograms.kg-1.min-1 for weaning. But we experienced no serious complications such as hypoxemia or perioperative myocardial infarction.

L9 ANSWER 20 OF 22 CAPLUS COPYRIGHT 2002 ACS
AN 1990:417906 CAPLUS
DN 113:17906
TI Use of organic nitro compounds for the prophylaxis and therapy of porcine stress syndrome
IN Gessert, Bernd
PA CP-Pharma Handelsgesellschaft m.b.H., Fed. Rep. Ger.; IG Spruehtechnik G.m.b.H.

SO Ger. Offen., 2 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3812265	A1	19891102	DE 1988-3812265	19880413

AB Dermal application (e.g., ointments or sprays) of org. nitrates (e.g., **nitroglycerin**, isosorbide dinitrate) is effective for the **prophylaxis** or therapy of porcine stress syndrome (**malignant** hyperthermia).
IT Swine
(**malignant** hyperthermia of, org. nitrates for **inhibition** of)
IT Fever and Hyperthermia
(**malignant**, org. nitrates for **prophylaxis** and therapy of, in swine)
IT 78-11-5, Pentaerythritol tetranitrate 87-33-2, Isosorbide dinitrate 1607-17-6, Pentaerythritol **trinitrate** 7697-37-2D, Nitric acid, esters 15825-70-4, Mannitol hexanitrate 16051-77-7, Isosorbide mononitrate
RL: BIOL (Biological study)
(**malignant** hyperthermia in swine **inhibition** by)

L9 ANSWER 21 OF 22 MEDLINE DUPLICATE 11
AN 85302825 MEDLINE
DN 85302825 PubMed ID: 3929508
TI [Controlled arterial hypotension using nitroglycerin in brain surgery]. Upravliaemaia arterial'naia gipotoniia s pomoshch'iu nitroglitserina pri operatsiiakh na golovnom mozge.
AU Zozulia Iu A; Rodionov A G
SO ZHURNAL VOPROSY NEIROKHIRURGII IMENI N. N. BURDENKO, (1985 Jul-Aug) (3) 37-40.
Journal code: 7809757. ISSN: 0042-8817.
CY USSR
DT Journal; Article; (JOURNAL ARTICLE)
LA Russian
FS Priority Journals
EM 198510
ED Entered STN: 19900320
Last Updated on STN: 20000303
Entered Medline: 19851009
AB Artificial hypotension induced by 0.01% **nitroglycerin** solution was applied in 60 operations on the brain. It contributed to the creation of optimum conditions for radical removal of **tumors** and exclusion of vascular aneurysms, **reduction** of blood loss, and a decrease in the number of blood transfusion. The efficacy, adequate control, safety, and attainability of the method allowed it to be recommended for use in neurosurgical practice when necessary.

L9 ANSWER 22 OF 22 MEDLINE DUPLICATE 12
AN 83290378 MEDLINE
DN 83290378 PubMed ID: 6411662
TI Effect of tumor blood flow manipulations on radiation response.
AU Pallavicini M G; Hill R P
SO INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (1983 Sep) 9 (9) 1321-5.
Journal code: 7603616. ISSN: 0360-3016.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198310

ED Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19831028

AB The effect of anesthestics and several vasoactive agents on the blood flow, temperature, and radiation response of the solid murine KHT sarcoma was evaluated to better understand the relationship of **tumor** blood flow and the proportion of hypoxic cells. **Tumor** blood flow, assessed by 133-Xenon clearance, decreased by 59 and 24% following treatment with pentobarbital and urethane, respectively. In addition, both drugs **reduced** body and **tumor** temperature. Metaraminol, a sympathomimetic agent, and **nitroglycerin** also **reduced** **tumor** blood flow by 40 and 12%, respectively. **Tumor** irradiation response following drug treatment was quantitated by an in vitro agar assay. Results indicate that drug-induced **reductions** in **tumor** blood flow generally result in an increase in the apparent **tumor** cell hypoxic fraction.

```
=> d que
L1             1 SEA FILE=REGISTRY GLYCERYL TRINITRATE/CN
L2               SEL  L1 1- CHEM :      77 TERMS
L3        273142 SEA L2/BI
L4         32678 SEA L3 (L) (CANCER? OR ANTICANCER? OR ANTINEOPLASTIC? OR
                 ANTITUMOR? OR TUMOR? OR MALIGNAN?)
L5        315922 SEA (CANCER? OR MALIGNAN? OR TUMOR? OR NEOPLAS?) (10A)
                 (PREVENT? OR PROPHYLA? OR REDUC? OR INHIBIT?)
L6          5062 SEA L4 AND L5
L7          4551 SEA (TRINITRATE OR GLYCERYL NITRATE OR GTN OR NITROGLYCERIN#
                 OR NITROGLYCEROL OR NITROGLYN) (35A) (PREVENT? OR PROPHYLA? OR
                 REDUC? OR INHIBIT?)
L8            42 SEA L7 AND L6
L9            22 DUP REM L8 (20 DUPLICATES REMOVED)
L11         5056 SEA L6 NOT (GTN OLIGODEOXY?)
L12         4804 SEA L11 NOT (NG (4A) ARGININE)
L13           52 SEA (TRINITRATE OR GLYCERYL NITRATE OR NITROGLYCERIN# OR
                 NITROGLYCEROL OR NITROGLYN) AND L12
L14           36 SEA L13 NOT L9
L15           23 DUP REM L14 (13 DUPLICATES REMOVED)

=> d 1-23 bib ab kwic

L15  ANSWER 1 OF 23     MEDLINE
AN   2002470963     MEDLINE
DN   22218015   PubMed ID: 12107174
TI   Oxygen-mediated regulation of tumor cell invasiveness. Involvement of a
     nitric oxide signaling pathway.
AU   Postovit Lynne-Marie; Adams Michael A; Lash Gendie E; Heaton Jeremy P;
     Graham Charles H
CS   Department of Anatomy and Cell Biology, Queen's University, Kingston,
     Ontario K7L 3N6, Canada.
SO   JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Sep 20) 277 (38) 35730-7.
     Journal code: 2985121R. ISSN: 0021-9258.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200210
ED   Entered STN: 20020917
     Last Updated on STN: 20021026
     Entered Medline: 20021024
AB   Tumor hypoxia is associated with a poor prognosis for patients
     with various cancers, often resulting in an increase in
     metastasis. Moreover, exposure to hypoxia increases the ability of breast
     carcinoma cells to invade the extracellular matrix, an important aspect of
     metastasis. Here, we demonstrate that the hypoxic up-regulation of
     invasiveness is linked to reduced nitric oxide signaling. Incubation of
     human breast carcinoma cells in 0.5% versus 20% oxygen increased their in
     vitro invasiveness and their expression of the urokinase receptor, an
     invasion-associated molecule. These effects of hypoxia were inhibited by
     nitric oxide-mimetic drugs; and in a manner similar to hypoxia,
     pharmacological inhibition of nitric oxide synthesis increased urokinase
     receptor expression. The nitric oxide signaling pathway involves
     activation of soluble guanylyl cyclase (sGC) and the subsequent activation
     of protein kinase G (PKG). Culture of tumor cells under hypoxic
     conditions (0.5% versus 20% oxygen) resulted in lower cGMP levels, an
     effect that could be prevented by incubation with glyceryl
     trinitrate. Inhibition of sGC activity with a selective blocker or
     with the heme biosynthesis inhibitor desferrioxamine increased urokinase
     receptor expression. These compounds also prevented the glyceryl
     trinitrate-mediated suppression of urokinase receptor expression
     in cells incubated under hypoxic conditions. In contrast, direct
```

activation of PKG using 8-bromo-cGMP prevented the hypoxia- and desferrioxamine-induced increases in urokinase receptor expression as well as the hypoxia-mediated enhanced invasiveness. Further involvement of PKG in the regulation of invasion-associated phenotypes was established using a selective PKG inhibitor, which alone increased urokinase receptor expression. These findings reveal that an important mechanism by which hypoxia increases **tumor** cell invasiveness (and possibly metastasis) requires **inhibition** of the nitric oxide signaling pathway involving sGC and PKG activation.

AB **Tumor** hypoxia is associated with a poor prognosis for patients with various **cancers**, often resulting in an increase in metastasis. Moreover, exposure to hypoxia increases the ability of breast carcinoma cells to invade. . . signaling pathway involves activation of soluble guanylyl cyclase (sGC) and the subsequent activation of protein kinase G (PKG). Culture of **tumor** cells under hypoxic conditions (0.5% versus 20% oxygen) resulted in lower cGMP levels, an effect that could be prevented by incubation with **glyceryl trinitrate**. Inhibition of sGC activity with a selective blocker or with the heme biosynthesis inhibitor desferrioxamine increased urokinase receptor expression. These compounds also prevented the **glyceryl trinitrate**-mediated suppression of urokinase receptor expression in cells incubated under hypoxic conditions. In contrast, direct activation of PKG using 8-bromo-cGMP prevented. . . selective PKG inhibitor, which alone increased urokinase receptor expression. These findings reveal that an important mechanism by which hypoxia increases **tumor** cell invasiveness (and possibly metastasis) requires **inhibition** of the nitric oxide signaling pathway involving sGC and PKG activation.

L15 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2001:798077 CAPLUS
DN 135:339243
TI Formulations and methods of using nitric oxide mimetics against a malignant cell phenotype
IN Adams, Michael A.; Graham, Charles H.; Heaton, Jeremy P. W.; Postovit, Lynne-Marie
PA Queen's University at Kingston, Can.
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001080890	A2	20011101	WO 2001-CA566	20010426
	WO 2001080890	A3	20020808		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002040059	A1	20020404	US 2001-842547	20010426
PRAI	US 2000-199757P	P	20000426		
	US 2001-277469P	P	20010321		

AB Methods and formulations for **inhibiting** and **preventing** a **malignant** cell phenotype by administering to cells a low dose of a nitric oxide mimetic are provided. Administration of the nitric oxide mimetic inhibits metastases and development of resistance to **antitumor** agents in the cells and delays or reduces development of drug tolerance. A nitric oxide mimetic is coadministered with a compd.

that inhibits cyclic nucleotide degrdn. For example, the resistance of MDA-MB-231 breast **cancer** cells to doxorubicin was detd. following culture in 20% or 1% oxygen by counting the no. of colonies formed. Following incubation for 24 h, the cells were exposed to diluent (control), 25 .mu.M doxorubicin, 25 .mu.M doxorubicin plus 10-6 M **glyceryl trinitrate** or 25 .mu.M doxorubicin plus 10-10 **glyceryl trinitrate** for 1 h. The surviving cells under each condition was detd. by counting the no. of colonies that survived without doxorubicin exposure.

AB Methods and formulations for **inhibiting** and **preventing** a **malignant** cell phenotype by administering to cells a low dose of a nitric oxide mimetic are provided. Administration of the nitric oxide mimetic inhibits metastases and development of resistance to **antitumor** agents in the cells and delays or reduces development of drug tolerance. A nitric oxide mimetic is coadministered with a compd. that inhibits cyclic nucleotide degrdn. For example, the resistance of MDA-MB-231 breast **cancer** cells to doxorubicin was detd. following culture in 20% or 1% oxygen by counting the no. of colonies formed. Following incubation for 24 h, the cells were exposed to diluent (control), 25 .mu.M doxorubicin, 25 .mu.M doxorubicin plus 10-6 M **glyceryl trinitrate** or 25 .mu.M doxorubicin plus 10-10 **glyceryl trinitrate** for 1 h. The surviving cells under each condition was detd. by counting the no. of colonies that survived without doxorubicin exposure.

IT Drug resistance
(antitumor, **prevention** of; formulations and methods of using nitric oxide mimetics against **malignant** cell phenotype)

IT Mammary gland
(carcinoma, metastasis, **inhibitors**; formulations and methods of using nitric oxide mimetics against **malignant** cell phenotype)

IT Nucleotides, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cyclic, degrdn., **inhibitors** of; formulations and methods of using nitric oxide mimetics against **malignant** cell phenotype)

IT Prostate gland
(**neoplasm**, **inhibitors**; formulations and methods of using nitric oxide mimetics against **malignant** cell phenotype)

IT Antitumor agents
(resistance to, **prevention** of; formulations and methods of using nitric oxide mimetics against **malignant** cell phenotype)

IT **55-63-0**, **Glyceryl trinitrate** 14402-89-2, Sodium nitroprusside
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulations and methods of using nitric oxide mimetics against **malignant** cell phenotype)

IT 127464-60-2, Vascular endothelial growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; formulations and methods of using nitric oxide mimetics against **malignant** cell phenotype)

L15 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2001:564844 CAPLUS
DN 135:147409
TI Xylose compounds for the treatment of proliferative disorders
IN Magnusson, Goeran; Belting, Mattias; Falk, Niklas; Fransson, Lars-Ake; Mani, Katrin
PA Xylogen AB, Swed.; Magnusson Hall, Pia Margareta
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001054702	A1	20010802	WO 2001-SE167	20010130
	W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1251859	A1	20021030	EP 2001-902926	20010130
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	SE 2000-303	A	20000131		
	WO 2001-SE167	W	20010130		

OS MARPAT 135:147409

AB An antiproliferative compn. comprises a xylose compd. and at least one antitumor agent selected from a polyamine synthesis inhibitor, polyamine cellular uptake inhibitor, polyamine degrdn. promoter, and epoxygenase inducer. Combination of xylose compds. and antitumor agent(s) is being selected such that a synergistic antiproliferative activity is accomplished. A method for treatment of proliferative disorders, particularly tumor diseases, comprises administering a combination of xylose compds. and antitumor agent(s) at a dose in the range of 0.001-100 mg/kg. For example, a compn. contains 6-hydroxy-2-naphthalenyl-.beta.-D-xylopyranoside, suramin, and .alpha.-difluoromethylornithine.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Intestine, **neoplasm**
(colon, **inhibitors**; synergistic antiproliferative compns. contg. xyloside and antitumor agents)

IT Liver, **neoplasm**
(hepatoma, **inhibitors**; synergistic antiproliferative compns. contg. xyloside and antitumor agents)

IT Brain, **neoplasm**
Lung, **neoplasm**
Stomach, **neoplasm**
(**inhibitors**; synergistic antiproliferative compns. contg. xyloside and antitumor agents)

IT Mammary gland
Prostate gland
(**neoplasm**, **inhibitors**; synergistic antiproliferative compns. contg. xyloside and antitumor agents)

IT **55-63-0**, **Nitroglycerin** 71-44-3, Spermine 145-63-1, Suramin 25717-80-0, Molsidomine 33876-97-0, Linsidomine 70052-12-9, .alpha.-Difluoromethylornithine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic antiproliferative compns. contg. xyloside and **antitumor** agents)

L15 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2001:564822 CAPLUS
DN 135:132469
TI Method for using potassium channel activation for delivering a medicant to an abnormal brain region and/or a malignant tumor
IN Black, Keith L.; Ningaraj, Nagendra S.
PA Cedars-Sinai Medical Center, USA
SO PCT Int. Appl., 72 pp.

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001054680	A2	20010802	WO 2001-US2742	20010126
	WO 2001054680	A3	20020627		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	EP 1251840	A2	20021030	EP 2001-905141	20010126

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI	US 2000-491500	A	20000126
	US 2000-615854	A	20000714
	WO 2001-US2742	W	20010126

AB Disclosed are methods of selectively delivering a medicant to an abnormal brain region and/or to a malignant tumor in a mammalian subject, including a human. A medicant is administered simultaneously or substantially simultaneously with a calcium- or ATP-dependent potassium channel [KCa or KATP] activator (other than bradykinin or a bradykinin analog), such as a direct potassium channel agonist or an indirect potassium channel activator, such as an activator of sol. guanylyl cyclase (e.g., nitric oxide or a nitric oxide donor) or an activator of cGMP-dependent protein kinase, whereby the medicant is delivered selectively to the cells of the abnormal brain region and/or to the tumor, compared to normal tissues. Thus, among the disclosures is a method of treating a malignant tumor in a human subject. Also disclosed are pharmaceutical compns. that combine a potassium channel activator together with a medicant and a kit for enhancing the delivery of a medicant to an abnormal brain region and/or to a malignant tumor.

IT Intestine, **neoplasm**
(colon, **inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT Intestine, **neoplasm**
(colorectal, **inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT Brain, **neoplasm**
(ependymoma, **inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT Liver, **neoplasm**
(hepatoma, **inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT Bone, **neoplasm**
Brain, **neoplasm**
Lung, **neoplasm**
Ovary, **neoplasm**
Skin, **neoplasm**
Stomach, **neoplasm**

Uterus, **neoplasm**
(**inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT Head
Mammary gland
Prostate gland
Spinal cord
(**neoplasm**, **inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT Nerve, **neoplasm**
(neuroblastoma, **inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT Intestine, **neoplasm**
(rectum, **inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT Antitumor agents
(thorax **tumor inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT Thorax
(**tumor inhibitors**; method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a malignant tumor)

IT **55-63-0**, **Nitroglycerin** 58-82-2, Bradykinin 78-11-5, Pentaerythrityl tetranitrate 87-33-2, Isosorbide dinitrate 10102-43-9D, Nitric oxide, adducts 14402-89-2, Sodium nitroprusside 16051-77-7, Isosorbide 5-mononitrate 25717-80-0, Molsidomine 32266-35-6, dibutyrylcyclic GMP 33876-97-0, Linsidomine 51209-75-7, S-Nitrosocysteine 57564-91-7, S-Nitrosoglutathione 67776-06-1, S-Nitroso-N-acetyl-D,L-penicillamine 83701-22-8, Minoxidil sulfate 92382-74-6, DEA/NO 132722-74-8, Pirsidomine 136587-13-8, Spermine-NONOate 146672-58-4 146724-94-9, Diethylamine-NONOate 146724-95-0 153587-01-0, NS-1619 170632-47-0, YC-1 178948-42-0 227757-99-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for using potassium channel activation with guanylyl cyclase and cGMP-dependent protein kinase activators such as nitric oxide donors for delivering a medicant to abnormal brain region and/or a **malignant tumor**)

L15 ANSWER 5 OF 23 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-326813 [34] WPIDS
CR 1995-160506 [21]; 1995-336803 [43]; 1996-277341 [28]; 1996-286350 [29]; 1996-476834 [47]; 1996-485456 [48]; 1997-511825 [47]; 1998-192229 [17]; 2000-618040 [51]
DNN N2001-234930 DNC C2001-100294
TI Polymeric compositions capable of releasing nitric oxide, used to **reduce** risk of restenosis after angioplasty, metastasis in **cancer** patients, treat male impotence, coat prostheses and medical implants.
DC B04 B05 P34
IN AKAMATSU, M; KEEFER, L K; ROLLER, P P; SAAVEDRA, J E

PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI US 6200558 B1 20010313 (200134)* 14p
ADT US 6200558 B1 CIP of US 1993-121169 19930914, US 1997-837812 19970422
FDT US 6200558 B1 CIP of US 5525357
PRAI US 1997-837812 19970422; US 1993-121169 19930914
AB US 6200558 B UPAB: 20020603
NOVELTY - Polymeric compositions capable of releasing nitric oxide comprise a biopolymeric backbone and at least one nitric oxide-releasing N2O2- functional group (NONOate).

DETAILED DESCRIPTION - Polymeric compositions capable of releasing nitric oxide comprise: (i) biopolymeric backbone of a tissue-specific antibody or its fragment, a cell-specific antibody or its fragment, a **tumor**-specific antibody or its fragment, a protein containing a recognition sequence of a receptor ligand interaction favorable to cell or tissue-selective attachment that includes at least one amino and/or carboxyl group; and (ii) at least one nitric oxide-releasing N2O2-functional group chosen from (X((O)NO)), X(N(O)NO) or (N(O)NO)X covalently bonded to the polymeric composition at one or more of the amino and/or carboxyl groups through the nucleophilic or electrophilic organic group.

X = nucleophilic or electrophilic organic group.

ACTIVITY - Vasotropic; cytostatic; gynecological.

MECHANISM OF ACTION - None given.

USE - The polymeric compositions are used in pharmaceutical compositions and to treat biological disorders in which administration of nitric oxide is therapeutic (claimed). They may be used as implants, patches, stents, liposomes, microparticles, microspheres, beads, powders, liquids, gels, monolithic resins and disks alone or attached to non-biopolymers. They may be used to reduce the risk of restenosis after angioplasty, to treat male impotence, to **reduce** the risk of metastasis in **cancer** patients, to coat prostheses and medical implants, such as breast implants, prior to surgical connection to the body to **reduce** the risk of associated solid-state carcinogenesis, to sensitize **cancer** cells to radiotherapy and to halt premature labor.

ADVANTAGE - The compositions are capable of spontaneously releasing nitric oxide under physiological conditions, not requiring activation through a redox reaction or electron transfer as is required for **glyceryl trinitrate** and sodium nitroprusside. The compositions can be applied with specificity to a biological site of interest, enhancing the selectivity of action of the NONOate.

Dwg.0/0

TI Polymeric compositions capable of releasing nitric oxide, used to **reduce** risk of restenosis after angioplasty, metastasis in **cancer** patients, treat male impotence, coat prostheses and medical implants.

AB . . .

nitric oxide comprise: (i) biopolymeric backbone of a tissue-specific antibody or its fragment, a cell-specific antibody or its fragment, a **tumor**-specific antibody or its fragment, a protein containing a recognition sequence of a receptor ligand interaction favorable to cell or tissue-selective. . . attached to non-biopolymers. They may be used to reduce the risk of restenosis after angioplasty, to treat male impotence, to **reduce** the risk of metastasis in **cancer** patients, to coat prostheses and medical implants, such as breast implants, prior to surgical connection to the body to **reduce** the risk of associated solid-state carcinogenesis, to sensitize **cancer** cells to radiotherapy and to halt premature labor.

ADVANTAGE - The compositions are capable of spontaneously releasing nitric oxide under physiological conditions, not requiring activation through a redox reaction or electron transfer as is required for **glyceryl trinitrate** and sodium nitroprusside. The compositions can be applied with specificity to a biological site of interest, enhancing the selectivity of. . .

TT TT: POLYMERISE COMPOSITION CAPABLE RELEASE NITRIC OXIDE **REDUCE** RISK AFTER ANGIOPLASTY METASTASIS **CANCER** PATIENT TREAT MALE IMPOTENCE COAT PROSTHESIS MEDICAL IMPLANT.

L15 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
AN 2002:50173 CAPLUS
DN 137:15382
TI Nitric oxide-mediated regulation of chemosensitivity in cancer cells
AU Matthews, Nicola E.; Adams, Michael A.; Maxwell, Lori R.; Gofton, Teneille E.; Graham, Charles H.
CS Department of Anatomy and Cell Biology, Queen's University, Kingston, ON, K7L 3N6, Can.
SO Journal of the National Cancer Institute (2001), 93(24), 1879-1885
CODEN: JNCIEQ; ISSN: 0027-8874
PB Oxford University Press
DT Journal
LA English
AB Hypoxia in **tumors** is assocd. with **malignant** progression, metastatic spread, and increased resistance to radiotherapy and chemotherapy. Mol. O2 is required for the cellular prodn. of nitric oxide (NO) by the enzyme NO synthase (NOS), and NO may block components of the adaptive response to hypoxia. Hence, the authors hypothesized that hypoxia increases drug resistance in **tumor** cells by **inhibiting** endogenous NO prodn. Human breast carcinoma (MDA-MB-231) and mouse melanoma (B16F10) cells were pre-exposed to 20% O2, 5% O2, or 1% O2, incubated with a pharmacol. inhibitor of endogenous NO prodn., and then treated with chemotherapeutic agents. Resistance was assessed by colony-formation assays, and Western blot anal. was used to measure NOS protein levels. All P values were 2-sided. Incubation of MDA-MB-231 **tumor** cells in 1% O2 maximally increased their resistance to doxorubicin and 5-fluorouracil by 8.5-fold (P = .002) and 2.3-fold (P = .002), resp., compared with incubation in 20% O2. B16F10 mouse melanoma cells preincubated in 1% O2 (vs. 20% O2) for 12 h exhibited a 2-fold increase in resistance to doxorubicin (P<.001). The rapid acquisition of drug resistance after exposure to 1% O2 could be mimicked by incubating the MDA-MB-231 cells for 12 h with the NOS inhibitor **NG**-monomethyl-L-Arg (five-fold increase; P<.001). Conversely, replacement of NO activity by the NO-mimetic **glyceryl trinitrate** (**GTN**) and diethylenetriamine NO adduct produced statistically significant attenuation in the development of resistance of 59% (P<.001) and 40% (P<.001), resp., in MDA-MB-231 cells. Treatment of B16F10 cells with **GTN** produced a 58% redn. in resistance (P<.001). MDA-MB-231 cells expressed all 3 isoforms of the NOS enzyme at levels that were not altered by exposure to hypoxia. NO mediates chemosensitivity in **tumor** cells, and hypoxia-induced drug resistance appears to result, in part, from downstream suppression of endogenous NO prodn. These results raise the possibility that administration of small doses of NO mimetics could be used as an adjuvant in chemotherapy.
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Hypoxia in **tumors** is assocd. with **malignant** progression, metastatic spread, and increased resistance to radiotherapy and chemotherapy. Mol. O2 is required for the cellular prodn. of nitric oxide (NO) by the enzyme NO synthase (NOS), and NO may block components of the adaptive response to hypoxia. Hence, the authors hypothesized that hypoxia increases drug resistance in **tumor** cells by **inhibiting** endogenous NO prodn. Human breast carcinoma (MDA-MB-231) and mouse melanoma (B16F10) cells were pre-exposed to 20% O2, 5% O2, or 1% O2, incubated with a pharmacol. inhibitor of endogenous NO prodn., and then treated with chemotherapeutic agents. Resistance was assessed by colony-formation assays, and Western blot anal. was used to measure NOS protein levels. All P values were 2-sided. Incubation of MDA-MB-231 **tumor** cells in 1% O2 maximally increased their

resistance to doxorubicin and 5-fluorouracil by 8.5-fold (P = .002) and 2.3-fold (P = .002), resp., compared with incubation in 20% O2. B16F10 mouse melanoma cells preincubated in 1% O2 (vs. 20% O2) for 12 h exhibited a 2-fold increase in resistance to doxorubicin (P<.001). The rapid acquisition of drug resistance after exposure to 1% O2 could be mimicked by incubating the MDA-MB-231 cells for 12 h with the NOS inhibitor **NG**-monomethyl-L-Arg (five-fold increase; P<.001). Conversely, replacement of NO activity by the NO-mimetic **glyceryl trinitrate** (**GTN**) and diethylenetriamine NO adduct produced statistically significant attenuation in the development of resistance of 59% (P<.001) and 40% (P<.001), resp., in MDA-MB-231 cells. Treatment of B16F10 cells with **GTN** produced a 58% redn. in resistance (P<.001). MDA-MB-231 cells expressed all 3 isoforms of the NOS enzyme at levels that were not altered by exposure to hypoxia. NO mediates chemosensitivity in **tumor** cells, and hypoxia-induced drug resistance appears to result, in part, from downstream suppression of endogenous NO prodn. These results raise the possibility that administration of small doses of NO mimetics could be used as an adjuvant in chemotherapy.

IT Hypoxia, animal
(hypoxia increased drug resistance in **tumor** cells by **inhibition** of endogenous NO prodn.)

IT Human
(hypoxia increased drug resistance in **tumor** cells by **inhibition** of endogenous NOS)

IT Antitumor agents
(resistance to; hypoxia increased drug resistance in **tumor** cells by **inhibition** of endogenous NO prodn.)

IT 10102-43-9, Nitrogen oxide (NO), biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypoxia increased drug resistance in **tumor** cells by **inhibition** of endogenous NO prodn.)

IT 125978-95-2, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypoxia increased drug resistance in **tumor** cells by **inhibition** of endogenous NOS)

L15 ANSWER 7 OF 23 MEDLINE DUPLICATE 2
AN 2001420877 MEDLINE
DN 21363147 PubMed ID: 11470751
TI **Nitroglycerin**: a NO donor **inhibits** TPA-mediated **tumor** promotion in murine skin.
AU Trikha P; Sharma N; Athar M
CS Department of Medical Elementology and Toxicology, Hamdard University, Hamdard Nagar, New Delhi 110 062, India.. prashant_trikha@hotmail.com
SO CARCINOGENESIS, (2001 Aug) 22 (8) 1207-11.
Journal code: 8008055. ISSN: 0143-3334.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010827
Last Updated on STN: 20010827
Entered Medline: 20010823
AB **Nitroglycerin** (**GTN**), a nitric oxide (NO) generating vasodilator has been used in the present study to assess the role of NO during **tumor** promotion in murine skin. Administration of **GTN** to 12-O tetradecanoyl phorbol 13-acetate (TPA)-treated mice resulted in a dose-dependent inhibition in the level of glutathione and the activity of antioxidant enzymes by approximately 16-40% of acetone-treated control. We also observed that **GTN** application led to a significant reduction in the ornithine decarboxylase (ODC) activity and decreased the rate of [3H]thymidine incorporation into

epidermal DNA when compared with the acetone-treated control (P < 0.001). Treatment of DMBA-initiated TPA-promoted mice with **GTN** increased the latency period, decreased the **tumor** incidence by 32% and there was a 2-fold decrease in **tumor** yield (**tumor** /mouse) as compared with the TPA (alone)-treated group by 20 weeks. From these data, it can be concluded that NO can abrogate the toxic and **tumor** promoting effects of TPA and **GTN** can be used as a chemopreventive agent to **inhibit tumorigenesis** in murine skin.

TI **Nitroglycerin**: a NO donor **inhibits** TPA-mediated **tumor** promotion in murine skin.

AB **Nitroglycerin** (**GTN**), a nitric oxide (NO) generating vasodilator has been used in the present study to assess the role of NO during **tumor** promotion in murine skin. Administration of **GTN** to 12-O tetradecanoyl phorbol 13-acetate (TPA)-treated mice resulted in a dose-dependent inhibition in the level of glutathione and the activity of antioxidant enzymes by approximately 16-40% of acetone-treated control. We also observed that **GTN** application led to a significant reduction in the ornithine decarboxylase (ODC) activity and decreased the rate of [3H]thymidine incorporation into epidermal DNA when compared with the acetone-treated control (P < 0.001). Treatment of DMBA-initiated TPA-promoted mice with **GTN** increased the latency period, decreased the **tumor** incidence by 32% and there was a 2-fold decrease in **tumor** yield (**tumor** /mouse) as compared with the TPA (alone)-treated group by 20 weeks. From these data, it can be concluded that NO can abrogate the toxic and **tumor** promoting effects of TPA and **GTN** can be used as a chemopreventive agent to **inhibit tumorigenesis** in murine skin.

CT Check Tags: Animal; Support, Non-U.S. Gov't
*Carcinogens: PD, pharmacology
Mice
*Nitric Oxide Donors: PD, pharmacology
***Nitroglycerin: PD, pharmacology**
Papilloma: CI, chemically induced
*Papilloma: PC, prevention & control
Skin Neoplasms: CI, chemically induced
*Skin Neoplasms: PC, prevention. . .

RN 16561-29-8 (Tetradecanoylphorbol Acetate); **55-63-0 (Nitroglycerin)**

L15 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2001:514258 CAPLUS
DN 136:116177
TI New findings on nitrogen monoxide research: From the physiology to the clinical practice
AU Mandalos, Achilleas; Mavracanas, Thomas; Zanos, Stavros; Miltsios, Constantinos; Bolomitis, Stephanos; Mironidou-Tzouveleki, Maria
CS Department of Pharmacology, Medical School, Aristotle University, Thessaloniki, Greece
SO Epitheorese Klinikes Farmakologias kai Farmakokinetikes (2001), 19(1), 5-24
CODEN: EKFFEO; ISSN: 1011-6575
PB Pharmakon-Press
DT Journal; General Review
LA Greek
AB A review. After elucidating to a great extent the functions and effects of nitric oxide (NO) on the cardiovascular system, researchers have turned to study other organ systems in which NO plays significant roles. NO is formed through the oxidn. of L-arginine, catalyzed by NO synthase (NOS). Three isoforms of the enzyme have been described; neuronal NOS (nNOS) is present in central and peripheral neurons, skeletal muscle, bronchoalveolar epithelial cells, and its activation depends upon the presence of calcium and calmodulin (CaM); endothelial NOS (eNOS) is found in vascular endothelial cells, and it is calcium- and calmodulin-dependent

as well; inducible NOS (iNOS) is not a structural constituent of the cells where it is located (i.e. macrophages, chondrocytes etc.); instead it is synthesized upon cell stimulation by cytokines or bacterial products, being independent of both calcium and CaM. Synthesis of NO begins with CaM binding to the NOS mol., followed by binding of L-binding to the NOS mol. NO has been implicated in carcinogenesis, as both as stimulant and a suppressive mol., with its role largely depending on its tissue concn. Cells being exposed for long intervals in high NO concns., as is the case with chronic inflammations, often show increased rates of mutations. In the initial stages of **tumor** growth, NO produced by macrophages' iNOS is toxic to **cancer** cells; however, in later stages, NO may increase vascular permeability, promote angiogenesis, and suppress cytotoxic T-lymphocyte activity. In addn., there are indications that NO **inhibits** the metastatic process, and leads to **cancer** cell death, inducing apoptotic processes. In what concerns the pulmonary endothelium, it has been shown that prolonged decrease in NO concn. is related to pulmonary hypertension. A possible therapeutic use of NO in acute respiratory distress syndrome has also been implied, which is thought to derive from vasodilatation, increase in alveolar ventilation, and inhibition of neutrophil activation. NO is widely recognized as one of the primary factors playing a significant role in the pathogenesis of inflammation. INOS-derived NO actions include vasodilatation and increase in local blood flow, and cytotoxicity, which is manifested either as a direct toxic action on cells, increasing intracellular cGMP levels, or indirectly, causing the formation of peroxinitrite (ONOO-), a free radical. This model has been confirmed by studying the pathogenetic mechanisms of a no. of inflammatory diseases, such as intestinal chronic inflammatory diseases, arthritis, and meningitis. No also plays a primary role in chronic inflammatory pain, through its involvement in apoptosis of anterior horn spinal neurons. In diabetes mellitus type I, cytokines produced during the autoimmune process, induces iNOS in beta-cells, resulting in increased concn. of NO, which inhibit synthesis and release of insulin. Moreover, it has been postulated, that insulin resistance in diabetes mellitus type II, involves a NO-dependent mechanism. NO plays an important role in migraine pain as well. It is well known that migraine patients often exhibit migraine attacks after taking nitrates. **Nitroglycerin** induces vasodilation in intracranial vessels, through NO release. Direct stimulation of perivascular sensory fibers by NO in cerebral ischemia depends on the time course of the ischemic event right after the induction of ischemia. No produced in endothelial cells induces vasodilatation, inhibits vessel obstruction by platelets and leukocytes, and deteriorates the neurotoxic results of free radical prodn. In later stages, high concns. of NO produced by both neuronal and non-neuronal cells, augment ischemic cell death, causing the release of peroxinitrite and inhibiting cellular metab. and DNA replication. Finally, NO, combined with a mitochondrial metabolic dysfunction and excitotoxic processes, seems to play an important role in Parkinson's disease (PD) pathogenesis. Excitotoxicity has emerged as a major mechanism of neurotoxicity, which is mediated by NMDA-receptors and a subsequent increase in intracellular calcium; increased calcium levels stimulate NOS activity and peroxinitrite prodn., which causes a variety of lesions in DNA, lipids, and protein constituents of neurons.

AB A review. After elucidating to a great extent the functions and effects of nitric oxide (NO) on the cardiovascular system, researchers have turned to study other organ systems in which NO plays significant roles. NO is formed through the oxidn. of L-arginine, catalyzed by NO synthase (NOS). Three isoforms of the enzyme have been described; neuronal NOS (nNOS) is present in central and peripheral neurons, skeletal muscle, bronchoalveolar epithelial cells, and its activation depends upon the presence of calcium and calmodulin (CaM); endothelial NOS (eNOS) is found in vascular endothelial cells, and it is calcium- and calmodulin-dependent as well; inducible NOS (iNOS) is not a structural constituent of the cells where it is located (i.e. macrophages, chondrocytes etc.); instead it is synthesized upon cell stimulation by cytokines or bacterial products,

being independent of both calcium and CaM. Synthesis of NO begins with CaM binding to the NOS mol., followed by binding of L-binding to the NOS mol. NO has been implicated in carcinogenesis, as both as stimulant and a suppressive mol., with its role largely depending on its tissue concn. Cells being exposed for long intervals in high NO concns., as is the case with chronic inflammations, often show increased rates of mutations. In the initial stages of **tumor** growth, NO produced by macrophages' iNOS is toxic to **cancer** cells; however, in later stages, NO may increase vascular permeability, promote angiogenesis, and suppress cytotoxic T-lymphocyte activity. In addn., there are indications that NO **inhibits** the metastatic process, and leads to **cancer** cell death, inducing apoptotic processes. In what concerns the pulmonary endothelium, it has been shown that prolonged decrease in NO concn. is related to pulmonary hypertension. A possible therapeutic use of NO in acute respiratory distress syndrome has also been implied, which is thought to derive from vasodilatation, increase in alveolar ventilation, and inhibition of neutrophil activation. NO is widely recognized as one of the primary factors playing a significant role in the pathogenesis of inflammation. INOS-derived NO actions include vasodilatation and increase in local blood flow, and cytotoxicity, which is manifested either as a direct toxic action on cells, increasing intracellular cGMP levels, or indirectly, causing the formation of peroxinitrite (ONOO-), a free radical. This model has been confirmed by studying the pathogenetic mechanisms of a no. of inflammatory diseases, such as intestinal chronic inflammatory diseases, arthritis, and meningitis. No also plays a primary role in chronic inflammatory pain, through its involvement in apoptosis of anterior horn spinal neurons. In diabetes mellitus type I, cytokines produced during the autoimmune process, induces iNOS in beta-cells, resulting in increased concn. of NO, which inhibit synthesis and release of insulin. Moreover, it has been postulated, that insulin resistance in diabetes mellitus type II, involves a NO-dependent mechanism. NO plays an important role in migraine pain as well. It is well known that migraine patients often exhibit migraine attacks after taking nitrates. **Nitroglycerin** induces vasodilation in intracranial vessels, through NO release. Direct stimulation of perivascular sensory fibers by NO in cerebral ischemia depends on the time course of the ischemic event right after the induction of ischemia. No produced in endothelial cells induces vasodilatation, inhibits vessel obstruction by platelets and leukocytes, and deteriorates the neurotoxic results of free radical prodn. In later stages, high concns. of NO produced by both neuronal and non-neuronal cells, augment ischemic cell death, causing the release of peroxinitrite and inhibiting cellular metab. and DNA replication. Finally, NO, combined with a mitochondrial metabolic dysfunction and excitotoxic processes, seems to play an important role in Parkinson's disease (PD) pathogenesis. Excitotoxicity has emerged as a major mechanism of neurotoxicity, which is mediated by NMDA-receptors and a subsequent increase in intracellular calcium; increased calcium levels stimulate NOS activity and peroxinitrite prodn., which causes a variety of lesions in DNA, lipids, and protein constituents of neurons.

L15 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
AN 2000:812175 CAPLUS
DN 134:95237
TI A blood-tumor barrier limits gene transfer to experimental liver cancer: the effect of vasoactive compounds
AU Bilbao, R.; Bustos, M.; Alzuguren, P.; Pajares, M. J.; Drozdzik, M.; Qian, C.; Prieto, J.
CS Department of Internal Medicine and Liver Unit, School of Medicine, University of Navarra, Pamplona, 31080, Spain
SO Gene Therapy (2000), 7(21), 1824-1832
CODEN: GETHEC; ISSN: 0969-7128
PB Nature Publishing Group
DT Journal
LA English

AB We have evaluated gene transfer efficiency to **tumor** nodules in diethylnitrosoamine (DENA)-induced hepatocellular carcinoma (HCC) in rats using adenoviral vectors administered by three different routes: intraportal, intra-arterial and intratumoral injection. Our results showed that intraportal infusion could not transduce **tumor** nodules greater than 1 mm in diam. while the intra-arterial route allowed transduction of nodules up to 2-5 mm in diam. **Tumors** greater than this size were resistant to transduction by intravascular route, but could be transduced by direct intratumoral injection, indicating that the obstacle **preventing** gene transfer to **tumor** cells was mainly at the level of **tumor** vasculature and not at the level of neoplastic cells. We have studied the extracellular matrix in **tumoral** lesions to assess whether nodules with different size and histol. pattern have different profiles in relation to transduction efficacy. Immunohistochem. detection showed a high expression of fibronectin (FN), laminin (LN) and .alpha.-smooth muscle actin (.alpha.-SMA) in those large HCC, which were resistant to adenoviral infection. Intra-arterial infusion of vasoactive compds. (histamine, angiotensin II or nitric oxide donor **nitroglycerin**) before vector administration enhanced gene transfer to **tumor** nodules that were poorly transduced without pre-treatment. **Nitroglycerin** was active to enhance transduction of large **tumors** with trabecular or pseudoglandular histol. pattern, which were impermeable to adenoviral vectors even after histamine or angiotensin treatments. Our data indicate the presence of a phys. barrier between blood and **neoplastic** cells, which **prevents** transduction of the **tumor** by vectors given by the intravascular route. The thickness and impermeability of the barrier increases as the **tumor** nodule grows. Vasoactive compds. may be of value in gene therapy of liver **cancer** by increasing transduction efficiency by intravascularly administered vectors.

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB We have evaluated gene transfer efficiency to **tumor** nodules in diethylnitrosoamine (DENA)-induced hepatocellular carcinoma (HCC) in rats using adenoviral vectors administered by three different routes: intraportal, intra-arterial and intratumoral injection. Our results showed that intraportal infusion could not transduce **tumor** nodules greater than 1 mm in diam. while the intra-arterial route allowed transduction of nodules up to 2-5 mm in diam. **Tumors** greater than this size were resistant to transduction by intravascular route, but could be transduced by direct intratumoral injection, indicating that the obstacle **preventing** gene transfer to **tumor** cells was mainly at the level of **tumor** vasculature and not at the level of neoplastic cells. We have studied the extracellular matrix in **tumoral** lesions to assess whether nodules with different size and histol. pattern have different profiles in relation to transduction efficacy. Immunohistochem. detection showed a high expression of fibronectin (FN), laminin (LN) and .alpha.-smooth muscle actin (.alpha.-SMA) in those large HCC, which were resistant to adenoviral infection. Intra-arterial infusion of vasoactive compds. (histamine, angiotensin II or nitric oxide donor **nitroglycerin**) before vector administration enhanced gene transfer to **tumor** nodules that were poorly transduced without pre-treatment. **Nitroglycerin** was active to enhance transduction of large **tumors** with trabecular or pseudoglandular histol. pattern, which were impermeable to adenoviral vectors even after histamine or angiotensin treatments. Our data indicate the presence of a phys. barrier between blood and **neoplastic** cells, which **prevents** transduction of the **tumor** by vectors given by the intravascular route. The thickness and impermeability of the barrier increases as the **tumor** nodule grows. Vasoactive compds. may be of value in gene therapy of liver **cancer** by increasing transduction efficiency by intravascularly administered vectors.

IT 51-45-6, Histamine, biological studies **55-63-0**, **Nitroglycerin** 11128-99-7, Angiotensin II
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(blood-**tumor** barrier limits gene transfer to exptl. liver **cancer**: effect of vasoactive compds.)

L15 ANSWER 10 OF 23 MEDLINE DUPLICATE 4
AN 2001062059 MEDLINE
DN 20432378 PubMed ID: 10974079
TI Effect of dietary vitamin E on spontaneous or nitric oxide donor-induced mutations in a mouse tumor model.
AU Sandhu J K; Haqqani A S; Birnboim H C
CS Department of Biochemistry, Microbiology, and Immunology, University of Ottawa, and the Ottawa Regional Cancer Centre, Ontario, Canada.
SO JOURNAL OF THE NATIONAL CANCER INSTITUTE, (2000 Sep 6) 92 (17) 1429-33. Journal code: 7503089. ISSN: 0027-8874.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001222
AB BACKGROUND: Vitamin E, an antioxidant, has been investigated for its effect on **cancer** incidence in humans, but no firm conclusions about a protective effect can be drawn from these studies. Recently, we reported a statistically significant correlation in the Mutatect mouse **tumor** model between the number of neutrophils and the frequency of mutation at the hypoxanthine phosphoribosyltransferase (hprt) locus. We have now used this model to investigate vitamin E's effect on the hprt mutation rate. METHODS: Mutatect cells were grown in mice as subcutaneous **tumors** for 2-3 weeks, the **tumor** cells were recovered, and 6-thioguanine-resistant (i.e., hprt mutant) colonies were scored. Myeloperoxidase activity was used as a measure of neutrophil infiltration. Vitamin E (2 IU/kg body weight) was provided in the diet for 3-4 weeks. In some experiments, **glyceryl trinitrate** (100 mg/kg body weight) was also administered as a source of nitric oxide. All statistical tests were two-sided. RESULTS: Mouse **tumors** from the Mutatect MN-11 cell line exhibited a 3.2-fold higher median mutation frequency than the same cells in culture (P:<. 0001); vitamin E reduced this frequency by 24.9% (P: =.01). Mutatect TM-28-derived **tumors** (which secrete interleukin 8) were heavily infiltrated with neutrophils and had a correspondingly high mutation frequency; in two separate experiments, vitamin E reduced the median mutation frequency by 68.9% (P: =.0019) and 84.1% (P: =.011) and myeloperoxidase levels by 75.3% (P: =.0002) and 75.5% (P: =.026), respectively. **Glyceryl trinitrate** increased the mutation frequency in MN-11 **tumors**, and vitamin E **reduced** the median frequency by 61.4% (P: =.058). CONCLUSIONS: Dietary vitamin E afforded strong protection against both spontaneously arising and nitric oxide-induced mutations. Two separate protective mechanisms by vitamin E may be operating: scavenging of a nitric oxide-related genotoxic species and altering the infiltration of neutrophils into **tumors**.
AB BACKGROUND: Vitamin E, an antioxidant, has been investigated for its effect on **cancer** incidence in humans, but no firm conclusions about a protective effect can be drawn from these studies. Recently, we reported a statistically significant correlation in the Mutatect mouse **tumor** model between the number of neutrophils and the frequency of mutation at the hypoxanthine phosphoribosyltransferase (hprt) locus. We have now. . . model to investigate vitamin E's effect on the hprt mutation rate. METHODS: Mutatect cells were grown in mice as subcutaneous **tumors** for 2-3 weeks, the **tumor** cells were recovered,

and 6-thioguanine-resistant (i.e., hprt mutant) colonies were scored. Myeloperoxidase activity was used as a measure of neutrophil infiltration. Vitamin E (2 IU/kg body weight) was provided in the diet for 3-4 weeks. In some experiments, **glyceryl trinitrate** (100 mg/kg body weight) was also administered as a source of nitric oxide. All statistical tests were two-sided. RESULTS: Mouse **tumors** from the Mutatect MN-11 cell line exhibited a 3.2-fold higher median mutation frequency than the same cells in culture (P:<. 0001); vitamin E reduced this frequency by 24.9% (P: =.01). Mutatect TM-28-derived **tumors** (which secrete interleukin 8) were heavily infiltrated with neutrophils and had a correspondingly high mutation frequency; in two separate experiments,. . . by 68.9% (P: =.0019) and 84.1% (P: =.011) and myeloperoxidase levels by 75.3% (P: =.0002) and 75.5% (P: =.026), respectively. **Glyceryl trinitrate** increased the mutation frequency in MN-11 **tumors**, and vitamin E **reduced** the median frequency by 61.4% (P: =.058). CONCLUSIONS: Dietary vitamin E afforded strong protection against both spontaneously arising and nitric. . . by vitamin E may be operating: scavenging of a nitric oxide-related genotoxic species and altering the infiltration of neutrophils into **tumors**
.

L15 ANSWER 11 OF 23 MEDLINE DUPLICATE 5
AN 2000388105 MEDLINE
DN 20344927 PubMed ID: 10884648
TI Cardiopulmonary bypass exacerbates oxidative stress but does not increase proinflammatory cytokine release in patients with diabetes compared with patients without diabetes: regulatory effects of exogenous nitric oxide.
CM Comment in: J Thorac Cardiovasc Surg. 2001 Mar;121(3):598
AU Matata B M; Galinanes M
CS Division of Cardiac Surgery, University of Leicester, Glenfield Hospital, Leicester, United Kingdom.
SO JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (2000 Jul) 120 (1) 1-11. Journal code: 0376343. ISSN: 0022-5223.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200008
ED Entered STN: 20000818
Last Updated on STN: 20010730
Entered Medline: 20000809
AB BACKGROUND: Cardiopulmonary bypass induces oxidative stress and a whole-body inflammatory reaction that are believed to increase surgical morbidity. OBJECTIVES: Our goal was to investigate the effect of nitric oxide supplementation on bypass-induced oxidative stress and inflammatory reaction in patients with and without diabetes undergoing elective coronary bypass graft surgery. METHODS: Patients with and without diabetes were randomized to receive an infusion of saline solution or the nitric oxide donor **nitroglycerin** at 1 microg. kg(-1). min(-1) starting 10 minutes before the initiation of cardiopulmonary bypass and then maintained for 4 hours (n = 10 per group). Serial blood samples were taken at various intervals and plasma was analyzed for markers of oxidative stress (lipid hydroperoxides, protein carbonyls, and protein nitrotyrosine) and inflammation (complement C3a, elastase, interleukin 8, and **tumor** necrosis factor alpha). RESULTS: Cardiopulmonary bypass significantly increased lipid hydroperoxides, protein carbonyls, protein nitrotyrosine, complement C3a, elastase, soluble E-selectin, interleukin 8, and **tumor** necrosis factor alpha in both groups. Infusion of **nitroglycerin** significantly **reduced** the increase in lipid hydroperoxides and protein carbonyls in patients who have diabetes without affecting levels in patients without diabetes. **Nitroglycerin** infusion markedly **reduced** protein

nitrotyrosine and **tumor** necrosis factor alpha levels in both groups. In contrast, **nitroglycerin** infusion significantly increased C3a in patients without diabetes and increased elastase and interleukin 8 levels in patients with diabetes. CONCLUSIONS: Cardiopulmonary bypass induces a greater oxidative stress in patients with diabetes than in those without diabetes, and the inflammatory reaction is qualitatively different in the 2 groups of patients. In addition, **nitroglycerin** reduces oxidative stress in patients with diabetes and differentially affects the inflammatory response to bypass both in patients with and in those without diabetes. The results have important implications with respect to the use of nitric oxide donors during cardiopulmonary bypass.

AB . . . METHODS: Patients with and without diabetes were randomized to receive an infusion of saline solution or the nitric oxide donor **nitroglycerin** at 1 microg. kg(-1). min(-1) starting 10 minutes before the initiation of cardiopulmonary bypass and then maintained for 4 hours. . . for markers of oxidative stress (lipid hydroperoxides, protein carbonyls, and protein nitrotyrosine) and inflammation (complement C3a, elastase, interleukin 8, and **tumor** necrosis factor alpha). RESULTS: Cardiopulmonary bypass significantly increased lipid hydroperoxides, protein carbonyls, protein nitrotyrosine, complement C3a, elastase, soluble E-selectin, interleukin 8, and **tumor** necrosis factor alpha in both groups. Infusion of **nitroglycerin** significantly **reduced** the increase in lipid hydroperoxides and protein carbonyls in patients who have diabetes without affecting levels in patients without diabetes. **Nitroglycerin** infusion markedly **reduced** protein nitrotyrosine and **tumor** necrosis factor alpha levels in both groups. In contrast, **nitroglycerin** infusion significantly increased C3a in patients without diabetes and increased elastase and interleukin 8 levels in patients with diabetes. CONCLUSIONS:. . . than in those without diabetes, and the inflammatory reaction is qualitatively different in the 2 groups of patients. In addition, **nitroglycerin** reduces oxidative stress in patients with diabetes and differentially affects the inflammatory response to bypass both in patients with and. . .

CT . . .

ME, metabolism
E-Selectin: BI, biosynthesis
Middle Age
Neutrophil Activation: DE, drug effects
Nitric Oxide: BL, blood
*Nitric Oxide: PD, pharmacology
Nitroglycerin: PD, pharmacology
*Oxidative Stress: DE, drug effects

RN 10102-43-9 (Nitric Oxide); **55-63-0 (Nitroglycerin)**

L15 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1999:688629 CAPLUS
DN 132:175414
TI Pharmacological modifications of the partial pressure of oxygen in murine tumors: evaluation using in vivo EPR oximetry
AU Gallez, Bernard; Jordan, Benedicte F.; Baudelet, Christine; Misson, Pierre-Damien
CS Laboratory of Medicinal Chemistry and Radiopharmacy, Universite Catholique de Louvain, Brussels, Belg.
SO Magnetic Resonance in Medicine (1999), 42(4), 627-630
CODEN: MRMEEN; ISSN: 0740-3194
PB Wiley-Liss, Inc.
DT Journal
LA English
AB EPR oximetry using an implantable paramagnetic probe was used to quantify the partial pressure of O (pO2) in tissues in a transplantable mouse tumor model after administration of 34 different vasodilators belonging to one of the following classes: angiotensin-converting enzyme inhibitors, Ca2+

antagonists, .alpha.-antagonists, K+ channel openers, .beta.-blockers, NO donors, and peripheral vasoactive agents. Twenty-four compds. were efficient in significantly increasing the local pO2 in a majority of tumors. The increase of local pO2 by the pharmacol. treatments was lower than that achieved by using O or carbogen breathing. This technique offers a tool for rapidly and accurately measuring treatment-induced modifications of pO2 in tumors.

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 9015-82-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; **tumor** oxygenation increase by vasodilators, including)

IT 50-60-2, Phentolamine **55-63-0**, **Nitroglycerin**
59-96-1, Phenoxybenzamine 87-33-2, Isosorbide dinitrate 98-92-0, Nicotinamide 364-98-7, Diazoxide 437-74-1, Xanthinol nicotinate 484-23-1, Dihydralazine 1028-33-7, Pentifylline 3703-79-5, Bamethan 6493-05-6, Pentoxifylline 13523-86-9, Pindolol 13655-52-2, Alprenolol 14402-89-2, Sodium nitroprusside 19216-56-9, Prazosin 21829-25-4, Nifedipine 23210-56-2, Ifenprodil 25717-80-0, Molsidomine 26839-75-8, Timolol 29122-68-7, Atenolol 34661-75-1, Urapidil 38304-91-5, Minoxidil 42399-41-7, Diltiazem 52468-60-7, Flunarizine 54767-75-8, Suloctidil 55242-55-2, Propentofylline 55837-25-7, Buflomedil 55985-32-5, Nicardipine 57149-07-2, Naftopidil 60560-33-0, Pinacidil 62571-86-2, Captopril 64706-54-3, Bepridil 75847-73-3, Enalapril 76547-98-3, Lisinopril
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**tumor** oxygenation increase by vasodilators, including)

L15 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1998:638153 CAPLUS
DN 130:20677
TI Estrogens and coronary artery reactivity in atherosclerotic monkeys
AU Williams, J. Koudy; Adams, Michael R.; Honore, Erika K.; Clarkson, Thomas B.
CS Comparative Medicine Clinical Research Center, Department of Comparative Medicine, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC, 27157-1040, USA
SO Endothelial Cell Research Series (1998), 3(Estrogen and the Vessel Wall), 225-236
CODEN: ECRSFY; ISSN: 1384-1270
PB Harwood Academic Publishers
DT Journal; General Review
LA English
AB A review, with 30 refs. It has been known for many years that sex hormones modulate vasodilator responses of arteries supplying the uterus with blood. Recently, it has been shown that sex hormones such as estrogen modulate vasomotor responses of other arteries, including coronary arteries. It is thought that modulation of vasodilator and constrictor responses of coronary arteries may be one mechanism by which estrogen affects the risk of coronary heart disease. Although several studies have examd. the effects (and potential mechanisms) of estrogen on vasodilator responses of nonatherosclerotic arteries, few have focused on estrogen's effects on atherosclerotic coronary arteries. In studies of ovariectomized atherosclerotic female cynomolgus monkeys, both long-term (2 yr) and short-term (20 min) estradiol treatment augments dilator responses to acetylcholine, but not **nitroglycerin**. Presumably, this indicates an effect of estradiol on endothelium-mediated dilator responses of coronary arteries. Addn. of the progestin medroxyprogesterone acetate diminishes the beneficial effect of conjugated equine estrogens on these dilator responses. This is significant because a progestin is usually added to estrogen replacement to **reduce**

the risk of endometrial and breast **cancer** assocd. with unopposed estrogen therapy. Studies in premenopausal female monkeys indicate that the effective plasma dose of estradiol is approx. 60-70 pg/mL; below that, estradiol does not affect vasodilation. When atherosclerotic, ovariectomized monkeys receive dietary lowering of cholesterol with and without hormone replacement therapy, vasodilator response improves little beyond that seen with lipid lowering alone. Furthermore, hormone status (being female and being premenopausal) has an effect on dilator responses of coronary arteries only up to a certain complexity of atherosclerotic lesion. The greatest effect of hormones are on moderately sized lesions with little calcification and necrosis. These last two studies may indicate some limitations of hormone therapy in affecting coronary vasomotor responses. However, estrogens remain an important modulator of arterial vasomotor responses and may play an important role in estrogen's effects on coronary heart disease risk.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review, with 30 refs. It has been known for many years that sex hormones modulate vasodilator responses of arteries supplying the uterus with blood. Recently, it has been shown that sex hormones such as estrogen modulate vasomotor responses of other arteries, including coronary arteries. It is thought that modulation of vasodilator and constrictor responses of coronary arteries may be one mechanism by which estrogen affects the risk of coronary heart disease. Although several studies have examd. the effects (and potential mechanisms) of estrogen on vasodilator responses of nonatherosclerotic arteries, few have focused on estrogen's effects on atherosclerotic coronary arteries. In studies of ovariectomized atherosclerotic female cynomolgus monkeys, both long-term (2 yr) and short-term (20 min) estradiol treatment augments dilator responses to acetylcholine, but not **nitroglycerin**. Presumably, this indicates an effect of estradiol on endothelium-mediated dilator responses of coronary arteries. Addn. of the progestin medroxyprogesterone acetate diminishes the beneficial effect of conjugated equine estrogens on these dilator responses. This is significant because a progestin is usually added to estrogen replacement to **reduce** the risk of endometrial and breast **cancer** assocd. with unopposed estrogen therapy. Studies in premenopausal female monkeys indicate that the effective plasma dose of estradiol is approx. 60-70 pg/mL; below that, estradiol does not affect vasodilation. When atherosclerotic, ovariectomized monkeys receive dietary lowering of cholesterol with and without hormone replacement therapy, vasodilator response improves little beyond that seen with lipid lowering alone. Furthermore, hormone status (being female and being premenopausal) has an effect on dilator responses of coronary arteries only up to a certain complexity of atherosclerotic lesion. The greatest effect of hormones are on moderately sized lesions with little calcification and necrosis. These last two studies may indicate some limitations of hormone therapy in affecting coronary vasomotor responses. However, estrogens remain an important modulator of arterial vasomotor responses and may play an important role in estrogen's effects on coronary heart disease risk.

L15 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
AN 1998:486907 CAPLUS
DN 129:198071
TI Estrogens, progestins, and coronary artery reactivity in atherosclerotic monkeys
AU Williams, J. Koudy; Delansorne, Remi; Paris, Jaques
CS The Comparative Medicine Clinical Research Center, Department of Comparative Medicine, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC, USA
SO Journal of Steroid Biochemistry and Molecular Biology (1998), 65(1-6), 219-224
CODEN: JSBBEZ; ISSN: 0960-0760
PB Elsevier Science Ltd.

DT Journal; General Review
LA English
AB A review with 30 refs. It has been known for many years that sex hormones modulate vasodilator responses of arteries supplying the uterus with blood. Recently, it has been shown that sex hormones such as estrogen modulate vasomotor responses of other arteries, including coronary arteries. It is thought that modulation of vasodilator and constrictor responses of coronary arteries may be one mechanism by which estrogen affects the risk of coronary heart disease. Although several studies have examd. the effects (and potential mechanisms) of estrogen on vasodilator responses of nonatherosclerotic arteries, few have focused on estrogen's effects on atherosclerotic coronary arteries. In studies of ovariectomized atherosclerotic female cynomolgus monkeys, both long-term (2 yr) and short-term (20 min) estradiol treatment augments dilator responses to acetylcholine, but not **nitroglycerin**. Presumably, this indicates an effect of estradiol on endothelium-mediated dilator responses of coronary arteries. Addn. of the progestin medroxyprogesterone acetate diminishes the beneficial effect of conjugated equine estrogens on these dilator responses. This is significant because a progestin is usually added to estrogen replacement to **reduce** the risk of endometrial and breast **cancer** assocd. with unopposed estrogen therapy. However, it would seem that not all progestins act similarly on vascular reactivity. Studies in monkeys indicate that addn. of progesterone or the progestin medroxyprogesterone acetate does not diminish the beneficial effects of estrogen on coronary dilator responses. Thus it would appear that different estrogen/progestin combinations may affect vascular reactivity in different manners, There is also an effort being made to examine the potential of different kinds of estrogens on cardiovascular risk. Studies in monkeys indicate that one of the estrogens found in conjugated equine estrogens (17 alpha-dihydroequilenin) has estrogen effects on vascular reactivity without having detrimental effects on uterine pathol. The isoflavones "plant estrogens" found in soy protein also have estrogenic effects on vascular reactivity and inhibition.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A review with 30 refs. It has been known for many years that sex hormones modulate vasodilator responses of arteries supplying the uterus with blood. Recently, it has been shown that sex hormones such as estrogen modulate vasomotor responses of other arteries, including coronary arteries. It is thought that modulation of vasodilator and constrictor responses of coronary arteries may be one mechanism by which estrogen affects the risk of coronary heart disease. Although several studies have examd. the effects (and potential mechanisms) of estrogen on vasodilator responses of nonatherosclerotic arteries, few have focused on estrogen's effects on atherosclerotic coronary arteries. In studies of ovariectomized atherosclerotic female cynomolgus monkeys, both long-term (2 yr) and short-term (20 min) estradiol treatment augments dilator responses to acetylcholine, but not **nitroglycerin**. Presumably, this indicates an effect of estradiol on endothelium-mediated dilator responses of coronary arteries. Addn. of the progestin medroxyprogesterone acetate diminishes the beneficial effect of conjugated equine estrogens on these dilator responses. This is significant because a progestin is usually added to estrogen replacement to **reduce** the risk of endometrial and breast **cancer** assocd. with unopposed estrogen therapy. However, it would seem that not all progestins act similarly on vascular reactivity. Studies in monkeys indicate that addn. of progesterone or the progestin medroxyprogesterone acetate does not diminish the beneficial effects of estrogen on coronary dilator responses. Thus it would appear that different estrogen/progestin combinations may affect vascular reactivity in different manners, There is also an effort being made to examine the potential of different kinds of estrogens on cardiovascular risk. Studies in monkeys indicate that one of the estrogens found in conjugated equine estrogens (17 alpha-dihydroequilenin)

has estrogen effects on vascular reactivity without having detrimental effects on uterine pathol. The isoflavones "plant estrogens" found in soy protein also have estrogenic effects on vascular reactivity and inhibition.

L15 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 7
AN 1996:361044 CAPLUS
DN 125:31830
TI **Inhibition** of the biologic activity of **tumor** necrosis factor maintains vascular endothelial cell function during hyperdynamic sepsis
AU Wang, Ping; Wood, Thomas J.; Zhou, Mian; Ba, Zheng F.; Chaudry, Irshad H.
CS School of Medicine, Rhode Island Hospital and Brown University, Providence, RI, 02903, USA
SO Journal of Trauma: Injury, Infection, and Critical Care (1996), 40(5), 694-701
CODEN: JOTRFA; ISSN: 1079-6061
PB Williams & Wilkins
DT Journal
LA English
AB Although vascular endothelial cell function (i.e., the release of endothelium-derived nitric oxide) decreases and plasma **tumor** necrosis factor (TNF) increases during sepsis, it is not known whether the elevated TNF is responsible for the depression of endothelial cell function under such conditions. The aim of this study, therefore, was to det. if inhibition of TNF biol. activity by polyethylene glycol dimerized conjugate of the recombinant human form of the p55 sol. TNF receptor (PEG-(rsTNF-R1)2) maintains endothelial function during sepsis. Rats were subjected to sepsis by cecal ligation and puncture (CLP). Immediately before the onset of sepsis, 600 .mu.g/rat PEG-(rsTNF-R1)2 or an equal vol. of saline was infused i.v. At 10 h after CLP (i.e., hyperdynamic sepsis), the thoracic aorta was isolated, cut into rings, and placed in organ chambers. Dose responses for an endothelium-dependent vasodilator, acetylcholine (ACh), and an endothelium-independent vasodilator, **nitroglycerin** (**NTG**), were detd. Endothelial cell structure was examd. by TEM. Endothelium-dependent vascular relaxation was depressed at 10 h after the onset of sepsis. Administration of PEG-(rsTNF-R1)2 before CLP, however, maintained ACh-induced relaxation. In contrast, no significant difference in **NTG**-induced relaxation was seen, irresp. of administration of PEG-(rsTNF-R1)2. Furthermore, the deterioration in endothelial structure during sepsis was prevented by PEG-(rsTNF-R1)2 pretreatment. Since administration of PEG-(rsTNF-R1)2 maintains vascular endothelial cell structure and function, it can be concluded that TNF plays a pivotal role in producing endothelial dysfunction during sepsis. Thus, pharmacol. agents that inhibit TNF biol. activity and/or its prodn. may be useful for protecting endothelial cells during sepsis.
TI **Inhibition** of the biologic activity of **tumor** necrosis factor maintains vascular endothelial cell function during hyperdynamic sepsis
AB Although vascular endothelial cell function (i.e., the release of endothelium-derived nitric oxide) decreases and plasma **tumor** necrosis factor (TNF) increases during sepsis, it is not known whether the elevated TNF is responsible for the depression of endothelial cell function under such conditions. The aim of this study, therefore, was to det. if inhibition of TNF biol. activity by polyethylene glycol dimerized conjugate of the recombinant human form of the p55 sol. TNF receptor (PEG-(rsTNF-R1)2) maintains endothelial function during sepsis. Rats were subjected to sepsis by cecal ligation and puncture (CLP). Immediately before the onset of sepsis, 600 .mu.g/rat PEG-(rsTNF-R1)2 or an equal vol. of saline was infused i.v. At 10 h after CLP (i.e., hyperdynamic sepsis), the thoracic aorta was isolated, cut into rings, and placed in organ chambers. Dose responses for an endothelium-dependent vasodilator, acetylcholine (ACh), and an endothelium-independent vasodilator,

nitroglycerin (**NTG**), were detd. Endothelial cell structure was examd. by TEM. Endothelium-dependent vascular relaxation was depressed at 10 h after the onset of sepsis. Administration of PEG-(rsTNF-R1)2 before CLP, however, maintained ACh-induced relaxation. In contrast, no significant difference in **NTG**-induced relaxation was seen, irresp. of administration of PEG-(rsTNF-R1)2. Furthermore, the deterioration in endothelial structure during sepsis was prevented by PEG-(rsTNF-R1)2 pretreatment. Since administration of PEG-(rsTNF-R1)2 maintains vascular endothelial cell structure and function, it can be concluded that TNF plays a pivotal role in producing endothelial dysfunction during sepsis. Thus, pharmacol. agents that inhibit TNF biol. activity and/or its prodn. may be useful for protecting endothelial cells during sepsis.

L15 ANSWER 16 OF 23 WPIDS (C) 2002 THOMSON DERWENT
AN 1995-179275 [24] WPIDS
DNN N1995-140819 DNC C1995-083035
TI Polymer bound nitric oxide and nucleophile adducts - provide controlled release of nitric oxide, for use in vaso- and broncho-dilation restenosis, cancer metastasis, etc..
DC A96 B04 B06 D22 P34
IN HRABIE, J A; KEEFER, L K; SAAVEDRA, J E
PA (KEEF-I) KEEFER L K
CYC 1
PI CA 2106105 A 19950315 (199524)* 44p
ADT CA 2106105 A CA 1993-2106105 19930914
PRAI CA 1993-2106105 19930914
AB CA 2106105 A UPAB: 19950626
Polymeric compsn. capable of releasing nitric oxide (NO), comprising a polymer and a NO releasing (NO)2- functional gp. bound to it, is new. The NO releasing gp. has the general formula (I): J = an organic or inorganic moiety, pref. not linked to the NO gps. through a C atom; M+ = a cation; x = valency of cation; a = 1 or 2; and b and c are the smallest integers which result in a neutral cpd.; with the cpd. pref. not being a salt of alanosine or dopastin.

USE - NO is involved in vaso- and broncho- dilation, neurotransmission, and immunological response, as well as gastric motility and nociception. Admin. of the adduct may be used in treating a variety of pulmonary disorders; NO effects penile erection, for treatment of impotence in men; inhibits platelet aggregation, this coupled with its cytostatic activity, is of use in preventing restenosis after angioplasty, or to inhibit cell division or platelet adhesion in damaged endothelial areas, minimising blockage; to **reduce** risk of metastasis in **cancer** patients; and to coat prostheses and medical implants, e.g. for the breast, before surgical connection, to reduce risk of solid state carcinogenesis. As a solid, the adduct can be used for implants, condoms, patches and prosthesis coatings, as well as for injectables and oral compsns.

ADVANTAGE - NO is a highly reactive gas with limited solubility in aq. media, and difficult to introduce reliably into biological systems. Prior art admin. as a prodrug, i.e., **glyceryl trinitrate** or Na nitroprusside, has disadvantages of tolerance development and toxicity of cyanides. The present adducts provide controlled release of NO for prolonged periods, and can be made site specific by use in solid form at the site required.

Dwg.0/3

AB . . .
in preventing restenosis after angioplasty, or to inhibit cell division or platelet adhesion in damaged endothelial areas, minimising blockage; to **reduce** risk of metastasis in **cancer** patients; and to coat prostheses and medical implants, e.g. for the breast, before surgical connection, to reduce risk of solid. . . limited solubility in aq. media, and difficult to introduce reliably into biological systems. Prior art admin. as a prodrug, i.e., **glyceryl trinitrate** or

Na nitroprusside, has disadvantages of tolerance development and toxicity of cyanides. The present adducts provide controlled release of NO. . .

L15 ANSWER 17 OF 23 MEDLINE DUPLICATE 8
AN 96043457 MEDLINE
DN 96043457 PubMed ID: 7485562
TI Various cells release a stable small molecule that inhibits endothelium-dependent relaxation.
AU Liu J J; Xie B; Thurlow P J; Wiley J S; Chen J R
CS Department of Cardiac Surgery, Austin Hospital, University of Melbourne, Heidelberg, Victoria, Australia.
SO AMERICAN JOURNAL OF PHYSIOLOGY, (1995 Oct) 269 (4 Pt 2) H1303-11. Journal code: 0370511. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
ED Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951212
AB Previous studies have shown that neutrophils release a stable factor that inhibits endothelium-dependent relaxation. In the present studies, the effects of supernatants derived from various cells on endothelium-dependent relaxation were studied. Cells were obtained from seven sources: human hematopoietic cells including mononuclear leukocytes (MONO), polymorphonuclear leukocytes (PMNs), and chronic lymphocytic leukemia (CLL) cells; cells of the cardiovascular system including human endothelial cell line ECV304, human smooth muscle cells, and rat myocardial cells; and the **tumor** cell line HPB. These isolated or cultured cells were incubated for 1 h in Krebs solution to release the factor. The results showed that the supernatants from 10(5) cells/ml of all cells except the **tumor** cell line HPB produced a potent **inhibitory** effect on endothelium-dependent relaxation of rat aortic rings in response to acetylcholine and Ca2+ ionophores A23187 and ionomycin but not on endothelium-independent relaxation to nitroprusside and **glyceryl trinitrate**. When the concentration increased to 10(6) cell/ml, the supernatants from the **tumor** cell line HPB also slightly but significantly **inhibited** endothelium-dependent relaxation. The potency order was PMNs = MONO = CLL cells > cardiac cells > smooth muscle cells > the endothelial cell line ECV304 > the **tumor** cell line HPB. It seems that the hematopoietic cells and the cardiac cells are more active in release of the factor. The effect of this factor was rapid in onset and hard to wash out. A cyclooxygenase inhibitor or a thromboxane A2-prostaglandin H2 receptor antagonist partially but significantly reduced the effect of the factor.(ABSTRACT TRUNCATED AT 250 WORDS)
AB . . . of the cardiovascular system including human endothelial cell line ECV304, human smooth muscle cells, and rat myocardial cells; and the **tumor** cell line HPB. These isolated or cultured cells were incubated for 1 h in Krebs solution to release the factor. The results showed that the supernatants from 10(5) cells/ml of all cells except the **tumor** cell line HPB produced a potent **inhibitory** effect on endothelium-dependent relaxation of rat aortic rings in response to acetylcholine and Ca2+ ionophores A23187 and ionomycin but not on endothelium-independent relaxation to nitroprusside and **glyceryl trinitrate**. When the concentration increased to 10(6) cell/ml, the supernatants from the **tumor** cell line HPB also slightly but significantly **inhibited** endothelium-dependent relaxation. The potency order was PMNs = MONO = CLL cells > cardiac cells > smooth muscle cells > the endothelial cell line ECV304 > the **tumor** cell line HPB. It seems that the hematopoietic cells and the cardiac cells are more active in release of the. . .

L15 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1996:20797 CAPLUS
DN 124:164696
TI Pharmacologic modification of tumor blood flow and interstitial fluid pressure in a human tumor xenograft: network analysis and mechanistic interpretation
AU Zlotecki, Robert A.; Baxter, Laurence T.; Boucher, Yves; Jain, Rakesh K.
CS Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, 02114, USA
SO Microvascular Research (1995), 50(3), 429-43
CODEN: MIVRA6; ISSN: 0026-2862
PB Academic
DT Journal
LA English
AB Various vasoactive agents have been used to modify **tumor** blood flow with the ultimate goal of improving **cancer** detection and treatment, with widely disparate results. Furthermore, the lack of mechanistic interpretations has hindered understanding of how these agents affect the different physiol. parameters involved in perfusion. Thus, there is a need to develop a unified framework for understanding the interrelated physiol. effects of pharmacol. and phys. agents. The goals of this study were (1) to develop a math. model which helps det. the location and magnitude of changes in the vascular resistance of **tumor** and normal tissues and (2) to test the model with the authors own exptl. studies and by comparison with results from the literature. The systemic and interstitial pressures and relative **tumor** blood flow were measured before and after administration of angiotensin II, epinephrine, norepinephrine, **nitroglycerin**, and hydralazine in SCID mice bearing LS174T human colon adenocarcinoma xenografts. A math. model was developed in analogy to elec. circuits which examd. the pressure, flow, and resistance relationships for arterial and venous segments of the vasculature of a **tumor** and surrounding normal tissue. Vasoconstrictor-induced increases in the mean arterial blood pressure led to increases in **tumor** blood flow and interstitial pressure with the magnitude of change dependent on the agent (percentage change in blood flow: angiotensin > epinephrine > norepinephrine). The vasodilating agents induced decreases in **tumor** blood flow in parallel to the induced decreases in the systemic pressure, but only the long-acting arterial vasodilator hydralazine was capable of effecting a decrease in **tumor** interstitial pressure. The model was also consistent with other data available in the literature on norepinephrine, pentoxifylline, nicotinamide, and hemodilution, and was useful in providing input as to the location and degree of the physiol. effects of these agents. The results of the data and model show that the steal phenomenon is the dominant mechanism for redistribution of host blood flow to the **tumor**. However, some degree of arterial control was present in the **tumors**. Moreover, the parallel increases in **tumor** interstitial pressure and blood flow contradict any hypothesis suggesting that elevated interstitial fluid pressure ppts. chronic vascular collapse, thus decreasing blood flow.
AB Various vasoactive agents have been used to modify **tumor** blood flow with the ultimate goal of improving **cancer** detection and treatment, with widely disparate results. Furthermore, the lack of mechanistic interpretations has hindered understanding of how these agents affect the different physiol. parameters involved in perfusion. Thus, there is a need to develop a unified framework for understanding the interrelated physiol. effects of pharmacol. and phys. agents. The goals of this study were (1) to develop a math. model which helps det. the location and magnitude of changes in the vascular resistance of **tumor** and normal tissues and (2) to test the model with the authors own exptl. studies and by comparison with results from the literature. The systemic and interstitial pressures and relative **tumor** blood flow were measured before and after administration of

angiotensin II, epinephrine, norepinephrine, **nitroglycerin**, and hydralazine in SCID mice bearing LS174T human colon adenocarcinoma xenografts. A math. model was developed in analogy to elec. circuits which examd. the pressure, flow, and resistance relationships for arterial and venous segments of the vasculature of a **tumor** and surrounding normal tissue. Vasoconstrictor-induced increases in the mean arterial blood pressure led to increases in **tumor** blood flow and interstitial pressure with the magnitude of change dependent on the agent (percentage change in blood flow: angiotensin > epinephrine > norepinephrine). The vasodilating agents induced decreases in **tumor** blood flow in parallel to the induced decreases in the systemic pressure, but only the long-acting arterial vasodilator hydralazine was capable of effecting a decrease in **tumor** interstitial pressure. The model was also consistent with other data available in the literature on norepinephrine, pentoxifylline, nicotinamide, and hemodilution, and was useful in providing input as to the location and degree of the physiol. effects of these agents. The results of the data and model show that the steal phenomenon is the dominant mechanism for redistribution of host blood flow to the **tumor**. However, some degree of arterial control was present in the **tumors**. Moreover, the parallel increases in **tumor** interstitial pressure and blood flow contradict any hypothesis suggesting that elevated interstitial fluid pressure ppts. chronic vascular collapse, thus decreasing blood flow.

IT Circulation
Neoplasm
Neoplasm inhibitors
Simulation and Modeling, biological
Vasoconstrictors
Vasodilators
(pharmacol. modification of **tumor** blood flow and interstitial fluid pressure in a human tumor xenograft with vasoactive agents in relation to network anal. and mechanistic interpretation)

IT 51-41-2, Norepinephrine 51-43-4, Epinephrine **55-63-0**, **Nitroglycerin** 86-54-4, Hydralazine 98-92-0, Nicotinamide 6493-05-6, Pentoxifylline 11128-99-7, Angiotensin-II
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. modification of **tumor** blood flow and interstitial fluid pressure in a human **tumor** xenograft with vasoactive agents in relation to network anal. and mechanistic interpretation)

L15 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1994:532130 CAPLUS
DN 121:132130
TI Administration of tumor necrosis factor-.alpha. in vivo depresses endothelium-dependent relaxation
AU Wang, Ping; Ba, Zheng F.; Chaudry, Irshad H.
CS Shock and Trauma Research Institute, Michigan State University, East Lansing, MI, 48824, USA
SO American Journal of Physiology (1994), 266(6, Pt. 2), H2535-41
CODEN: AJPHAP; ISSN: 0002-9513
DT Journal
LA English
AB Although depressed endothelium-dependent relaxation occurs during early sepsis, the precise mechanism responsible for this remains unknown. Because the elevated levels of plasma **tumor** necrosis factor (TNF) play a major role in the pathophysiol. of sepsis, it was investigated whether TNF-.alpha. administration alters endothelium-dependent relaxation. To study this, recombinant TNF-.alpha. (1.2.times.107 U/mg) was infused i.v. (0.25 mg/kg body wt) for 0.5 h in normal rats, and mean arterial pressure was monitored. At 1 h after the completion of TNF-.alpha. or vehicle infusion, the aorta and a pulmonary artery was isolated, cut into 2.5-mm rings, and placed in organ chambers.

Norepinephrine (2.times.10-7 M) was applied to achieve near-maximal contraction, and dose responses for an endothelium-dependent vasodilator, acetylcholine, and an endothelium-independent vasodilator, **nitroglycerin**, were detd. In addnl. studies, aortic rings from normal animals were incubated with TNF-.alpha. for 2 h in vitro, and vascular reactivity was detd. The TNF-.alpha. administration reduced acetylcholine-induced vascular relaxation both in vivo and in vitro. Such a redn. was sustained at least 80 min after the completion of 2 h incubation with TNF-.alpha.. In contrast, TNF did not alter **nitroglycerin**-induced vascular relaxation. Thus, TNF-.alpha. depresses endothelium-dependent relaxation in vitro as well as in vivo. Because TNF-.alpha. infusion increases plasma TNF levels without decreasing mean arterial pressure, the depressed endothelium-dependent relaxation obsd. during early sepsis may be due to the elevated circulating levels of TNF.

AB Although depressed endothelium-dependent relaxation occurs during early sepsis, the precise mechanism responsible for this remains unknown. Because the elevated levels of plasma **tumor** necrosis factor (TNF) play a major role in the pathophysiol. of sepsis, it was investigated whether TNF-.alpha. administration alters endothelium-dependent relaxation. To study this, recombinant TNF-.alpha. (1.2.times.107 U/mg) was infused i.v. (0.25 mg/kg body wt) for 0.5 h in normal rats, and mean arterial pressure was monitored. At 1 h after the completion of TNF-.alpha. or vehicle infusion, the aorta and a pulmonary artery was isolated, cut into 2.5-mm rings, and placed in organ chambers. Norepinephrine (2.times.10-7 M) was applied to achieve near-maximal contraction, and dose responses for an endothelium-dependent vasodilator, acetylcholine, and an endothelium-independent vasodilator, **nitroglycerin**, were detd. In addnl. studies, aortic rings from normal animals were incubated with TNF-.alpha. for 2 h in vitro, and vascular reactivity was detd. The TNF-.alpha. administration reduced acetylcholine-induced vascular relaxation both in vivo and in vitro. Such a redn. was sustained at least 80 min after the completion of 2 h incubation with TNF-.alpha.. In contrast, TNF did not alter **nitroglycerin**-induced vascular relaxation. Thus, TNF-.alpha. depresses endothelium-dependent relaxation in vitro as well as in vivo. Because TNF-.alpha. infusion increases plasma TNF levels without decreasing mean arterial pressure, the depressed endothelium-dependent relaxation obsd. during early sepsis may be due to the elevated circulating levels of TNF.

IT Sepsis and Septicemia
(endothelium-dependent relaxation in, **tumor** necrosis factor-.alpha. **inhibition** of)

IT Lymphokines and Cytokines
RL: BIOL (Biological study)
(**tumor** necrosis factor-.alpha., endothelium-dependent relaxation in sepsis **inhibition** by)

IT 10102-43-9, Nitric oxide, biological studies 90880-94-7, Endothelium-derived relaxing factor
RL: FORM (Formation, nonpreparative)
(formation of, **tumor** necrosis factor-.alpha. **inhibition** of, sepsis in relation to)

IT 51-84-3, Acetylcholine, biological studies
RL: BIOL (Biological study)
(vascular relaxation induced by, endothelium-dependent, **tumor** necrosis factor-.alpha. **inhibition** of, sepsis in relation to)

L15 ANSWER 20 OF 23 MEDLINE DUPLICATE 9
AN 90328449 MEDLINE
DN 90328449 PubMed ID: 1973879
TI [The importance of high-dose alpha-receptor blockade for blood volume and hemodynamics in pheochromocytoma].
Die Bedeutung einer hochdosierten alpha-Rezeptorenblockade fur Blutvolumen und Hamodynamik beim Phaochromocytom.

AU Grosse H; Schroder D; Schober O; Hausen B; Dralle H
CS Zentrum Anaesthesiologie, Abteilung I, Medizinische Hochschule Hannover.
SO ANAESTHESIST, (1990 Jun) 39 (6) 313-8.
Journal code: 0370525. ISSN: 0003-2417.
CY GERMANY, WEST: Germany, Federal Republic of
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA German
FS Priority Journals
EM 199008
ED Entered STN: 19901012
Last Updated on STN: 20020125
Entered Medline: 19900830
AB This prospective clinical study evaluates the possible beneficial effects of increased phenoxybenzamine dosage in the preoperative treatment of patients with pheochromocytoma. For this purpose total blood volume (TBV) prior to and after treatment with phenoxybenzamine and hemodynamic changes during surgery were determined in two groups of patients: group I (n = 12) received a mean dosage of 140 mg, group II (n = 12) 270 mg/day. The mean TBV in group I showed no changes after treatment with phenoxybenzamine, while the TBV in group II increased by 5.6 ml/kg body weight, corresponding to an increase in plasma volume (PV) of 10.2%. These changes were not significant, however. The intraoperative vasodilator requirement for the treatment of catecholamine induced hypertension during **tumor** manipulation was significantly less for group II: total nitroprusside administration averaged 8.7 mg in group I and 0.8 mg in group II (P less than 0.0005). Patients in group I received a total of 2.6 mg **nitroglycerin** compared with only 0.5 mg for patients in group II (P less than 0.005). In conclusion, preoperative treatment of patients with pheochromocytoma with increased dosages of phenoxybenzamine is beneficial to intraoperative management by decreasing hemodynamic instability due to **tumor** manipulation and following resection. This treatment was effective for **preventing** complications such as excessive tachycardia, cardiac arrhythmias, hypertensive crises, or left ventricular failure.
AB . . . of 10.2%. These changes were not significant, however. The intraoperative vasodilator requirement for the treatment of catecholamine induced hypertension during **tumor** manipulation was significantly less for group II: total nitroprusside administration averaged 8.7 mg in group I and 0.8 mg in group II (P less than 0.0005). Patients in group I received a total of 2.6 mg **nitroglycerin** compared with only 0.5 mg for patients in group II (P less than 0.005). In conclusion, preoperative treatment of patients with pheochromocytoma with increased dosages of phenoxybenzamine is beneficial to intraoperative management by decreasing hemodynamic instability due to **tumor** manipulation and following resection. This treatment was effective for **preventing** complications such as excessive tachycardia, cardiac arrhythmias, hypertensive crises, or left ventricular failure.

L15 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 10
AN 1991:99111 CAPLUS
DN 114:99111
TI Leukocyte-dependent and leukocyte-independent mechanisms of impairment of endothelium-mediated vasodilation
AU Lefer, Allan M.; Aoki, Nobuo
CS Jefferson Med. Coll., Thomas Jefferson Univ., Philadelphia, PA, 19107, USA
SO Blood Vessels (1990), 27(2-5), 162-8
CODEN: BLVSAB; ISSN: 0303-6847
DT Journal
LA English
AB Leukocytes release cytokines and oxygen-derived. free radicals upon activation. Both superoxide and **tumor** necrosis factor (TNF) **inhibited** endothelium-dependent vasodilation in the intact

circulation as well as in isolated blood vessels. Superoxide inactivates endothelium-derived relaxing factor (EDRF) rapidly, whereas TNF requireds 2 h to block EDRF release due to synthesis of adhesive proteins on the surface of neutrophils and/or the expression of their ligands on endothelial cells. Thus, vasodilation to acetylcholine is markedly attenuated by either superoxide or TNF, whereas the vasodilation to NaNO2 at pH 2.0 or to **nitroglycerin** is not affected. Superoxide dismutase restores acetylcholine responses to myocardial ischemia followed by reperfusion, whereas cycloheximide restores acetylcholine response to TNF. This occurs both in the isolated perfused rat heart (perfused without plasma or blood cells) and in isolated perfused cat carotid arteries. EDRF may be important in preserving integrity of vital tissues during ischemic states.

AB Leukocytes release cytokines and oxygen-derived. free radicals upon activation. Both superoxide and **tumor** necrosis factor (TNF) **inhibited** endothelium-dependent vasodilation in the intact circulation as well as in isolated blood vessels. Superoxide inactivates endothelium-derived relaxing factor (EDRF) rapidly, whereas TNF requireds 2 h to block EDRF release due to synthesis of adhesive proteins on the surface of neutrophils and/or the expression of their ligands on endothelial cells. Thus, vasodilation to acetylcholine is markedly attenuated by either superoxide or TNF, whereas the vasodilation to NaNO2 at pH 2.0 or to **nitroglycerin** is not affected. Superoxide dismutase restores acetylcholine responses to myocardial ischemia followed by reperfusion, whereas cycloheximide restores acetylcholine response to TNF. This occurs both in the isolated perfused rat heart (perfused without plasma or blood cells) and in isolated perfused cat carotid arteries. EDRF may be important in preserving integrity of vital tissues during ischemic states.

IT Leukocyte
(blood vessel relaxation **inhibition** by, superoxide and **tumor** necrosis factor in)

IT Lymphokines and Cytokines
RL: BIOL (Biological study)
(**tumor** necrosis factor, blood vessel dilaton **inhibition** by, leukocytes in)

IT 90880-94-7, Endothelium-derived relaxing factor
RL: BIOL (Biological study)
(blood vessel relaxation by, superoxide and **tumor** necrosis factor **inhibition** of)

L15 ANSWER 22 OF 23 CANCERLIT
AN 85302825 CANCERLIT
DN 85302825 PubMed ID: 3929508
TI [Controlled arterial hypotension using **nitroglycerin** in brain surgery].
Upravliaemaia arterial'naia gipotoniia s pomoshch'iu nitroglitserina pri operatsiiakh na golovnom mozge.
AU Zozulia Iu A; Rodionov A G
SO ZHURNAL VOPROSY NEIROKHIRURGII IMENI N. N. BURDENKO, (1985 Jul-Aug) (3) 37-40.
Journal code: 7809757. ISSN: 0042-8817.
CY USSR
DT Journal; Article; (JOURNAL ARTICLE)
LA Russian
FS MEDLINE; Priority Journals
OS MEDLINE 85302825
EM 198510
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB Artificial hypotension induced by 0.01% **nitroglycerin** solution was applied in 60 operations on the brain. It contributed to the creation of optimum conditions for radical removal of **tumors** and exclusion of vascular aneurysms, **reduction** of blood loss, and a

decrease in the number of blood transfusion. The efficacy, adequate control, safety, and attainability of the method allowed it to be recommended for use in neurosurgical practice when necessary.

TI [Controlled arterial hypotension using **nitroglycerin** in brain surgery].
Upravliaemaia arterial'naia gipotoniia s pomoshch'iu nitroglitserina pri operatsiiakh na golovnom mozge.

AB Artificial hypotension induced by 0.01% **nitroglycerin** solution was applied in 60 operations on the brain. It contributed to the creation of optimum conditions for radical removal of **tumors** and exclusion of vascular aneurysms, **reduction** of blood loss, and a decrease in the number of blood transfusion. The efficacy, adequate control, safety, and attainability of. . .

CT . . .
& control
English Abstract
Heart Rate
*Hypotension, Controlled
Injections, Intravenous
*Intracranial Aneurysm: SU, surgery
Intraoperative Complications: PC, prevention & control
Nitroglycerin: AD, administration & dosage
***Nitroglycerin: TU, therapeutic use**

RN **55-63-0 (Nitroglycerin)**

L15 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 11
AN 1983:572078 CAPLUS
DN 99:172078
TI Effect of tumor blood flow manipulations on radiation response
AU Pallavicini, Maria G.; Hill, Richard P.
CS Ontario Cancer Inst., Princess Margaret Hosp., Toronto, ON, M4X 1K9, Can.
SO Int. J. Radiat. Oncol., Biol., Phys. (1983), 9(9), 1321-5
CODEN: IOBPD3; ISSN: 0360-3016
DT Journal
LA English

AB Pentobarbital and urethane decreased **tumor** blood flow by 59 and 24%, resp., in mice with KHT sarcomas.. Metaraminol and **nitroglycerin** also decreased **tumor** blood flow by 40 and 12%, resp. Pretreatment with urethane, pentabarbital, or metaraminol increased **tumor** cell survival .apprx.3-fold following x-irradn. It appears likely that the **reduced tumor** blood flow induced by the anesthetics and metaraminol generally results in an increase in the apparent **tumor** cell hypoxic fraction.

AB Pentobarbital and urethane decreased **tumor** blood flow by 59 and 24%, resp., in mice with KHT sarcomas.. Metaraminol and **nitroglycerin** also decreased **tumor** blood flow by 40 and 12%, resp. Pretreatment with urethane, pentabarbital, or metaraminol increased **tumor** cell survival .apprx.3-fold following x-irradn. It appears likely that the **reduced tumor** blood flow induced by the anesthetics and metaraminol generally results in an increase in the apparent **tumor** cell hypoxic fraction.